REVIEW ARTICLE

Seizures in the Intensive Care Unit

S. K. Gupta, Ashok Parihar

Introduction

Seizures are a relatively common neurological complication in patients admitted to an Intensive Care Unit (ICU) environment. A review by Black et al. noted that approximately 12% of patients admitted with a non-neurological primary diagnosis incurred neurological events during their critical illness and out of this seizures constituted 28.1% (1). Since the incidence of seizures occurs most often in non-primary neurological patients, it is important for the general clinician, intensivist, and consulting neurologist to be well versed about seizures and their treatment in the ICU.

The ICU environment unfortunately presents unique challenges and difficulties with regards to the etiology, diagnosis and management of seizures. Because the patients are :–

(1) critically ill, frequently with multiple organ dysfunction presenting a variety of potential etiologies for cerebral disturbance.

(2) treated with sedatives and paralytics that prevent good neurological examination.

(3) presented with a variety of therapeutic drugs that may lower seizure threshold, and

(4) in an environment that hinders optimal EEG recording conditions.

All these factors work against the clinician in the prevention and management of seizures in an ICU setting.

Furthermore, significant clinical sequelae from seizures usually occur as a result of complications such as aspiration or trauma during the seizure, or cortical damage from a prolonged, unremitting course. Thus, it is mandatory to treat them vigorously and effectively.

Etiology

It must be emphasized that in the vast majority of cases, seizures occurring in the ICU are easily treated, and the focus of attention is toward identifying the etiology and to prevent recurrence. As listed below (Table 1) many conditions predispose to lowering of the seizure threshold. Since seizures may occur in virtually any individual given appropriate triggers, the clinician must play detective in determining which etiologic factor is responsible.

Some of the most common causes of seizures in a medical ICU are sepsis and cardiovascular disease (1). In addition, patients suffering from metabolic abnormalities and acute drug withdrawal also comprise a high percentage of patients with new-onset seizures (2). Metabolic abnormalities, in fact, may be responsible for up to 30-35% of seizures in critically ill patients (2). The most common specific etiologies include hyponatremia, uremia, and hypoglycemia. In patients with a primary neurological disorder, tumors, ischemic stroke, intracerebral hemorrhage, CNS infections,

From the Department of General Medicine, Government Medical College, Jammu (J&K) India.
Correspondence to : Dr. S. K. Gupta, Consultant Neurologist, 718-A, Gandhi Nagar, Jammu-180004 (J&K).

etc., all have a relatively high associated incidence of seizures.

Other causes of seizures in the ICU are drugs which are used commonly, though the medications rank fairly low as a risk for precipitating seizures. The large Boston Collaborative Drug Surveillance Programme evaluating the records of 32,812 in patients, found drug-induced seizures to occur in only 0.5% (3-5). Nevertheless, drugs with convulsant properties may precipitate seizures, in high risk patients such as the critically ill, and thus be particularly a problem in the ICU setting (6).

Among antimicrobials, the B-lactam compounds such as the penicillins and related antibiotics are frequently cited as posing a risk for inducing convulsions (0.5%), and care should be made in the critically ill patient to prescribe such medications only as necessary and in appropriate doses for the patient's medical condition (renal failure, congestive heart failure, liver disease) (3,7). Renal insufficiency, in particular, appears to be an important predisposing factor for B-lactam drug toxicity (7). Because of their action primarily as GABA antagonists, benzodiazepines, not phenytoin, should be considered as first line agents to combat B-lactam drug toxicity (7). Isoniazid (INH) is the second class of antimicrobials frequently associated with seizure toxicity occurring in 1-3% of patients, although quite uncommon in therapeutic doses (3). Of importance, seizures from this medication require administration of pyridoxine to circumvent the antagonism of pyridoxal phosphate by INH.

Another class of pharmaceuticals commonly linked to drug-induced seizure toxicity and as a cause of ICU admissions are the psychotropic agents, particularly the antidepressants. The relative risk for seizures ranges from 0.1-4% (8), and may be higher in select drugs. Although the vast majority of seizures induced by these medications occur following an overdose, the proconvulsant nature underlying their CNS effects is cause for concern when treating critical ill patients. Relative risk rates for some of these drugs have been assigned, and one should select from the low risk category if administering them to high risk patients. In particular, the serotonin selective reuptake inhibitors as well as trazodone, doxepin, and the MAO inhibitors all have very low potential for causing seizures, the tricyclics and buproprion have an intermediate risk, while maprotiline and amoxapine are considered high risk (8).

Other pharmaceuticals used in the ICU that have a noteworthy history of drug-induced seizures include the phenothiazine, chlorpromazine (risk 3-5%) (3,9,10) theophylline (risk 8-14% in theophylline toxic patients) (11-13) and the local anesthetics. Theophylline-induced seizures are distinct in that they may be refractory to the typical first line anticonvulsant agents such as the benzodiazepines, phenytoin, and phenobarbital (14, 15). Although local anesthetics as a group may induce seizures in toxic doses, lidocaine is most often the culprit due to its ubiquitous use as an antiarrhythmic and in a variety of forms for providing local anesthesia (spray, topical, subcutaneous, intravenous, epidural, intrathecal). The risk of seizures is dose dependent and correlates well with serum concentration. At therapeutic levels for the treatment of arrhythmias and as an anesthetic supplement (1-5 mg/L), the incidence of seizures is very low, whereas at concentrations of 8-12 mg/L, seizures become relatively common (16). Although convulsions are usually a result of high dose intravenous injection or directly into the CNS as in spinal anesthesia, seizures have been reported following intratracheal instillation for bronchoscopy or even after topical application (16-20).

In addition to medical causes, convulsive disorders rank high as a complication of head injury. Seizures can

manifest either early in the course (<1 week) or develop during the late recovery period or following discharge. Although a recent population-based study observed a 2.1% incidence of seizures following recovery from head injury (21), the incidence of early seizures appears to be higher. Almost half of the seizures occurred during the first 24 hrs. Once a seizure occurs, especially if it is of late onset (> 1 week), the risk of recurrence is high, approaching 90% (22). Late onset seizures are also a greater predictor of significant long term morbidity and poor outcome than those occurring early in the post-injury phase.

Table-1

Causes of Seizures in the ICU

1. **Primary Neurological Pathology**
   - Neurovascular disease – Stroke, – Malformation, – Hemorrhage, – Vasculitis
   - Tumors – Primary, – Secondary
   - CNS Infections :– – Abscess, – Meningitis, – Encephalitis, – Cerebral malaria
   - Primary Epilepsy
   - Metabolic disturbances
   - Head injury – Cerebral contusion, – Cerebral hemorrhage
2. **Complications of critical illness & management**
   - Hypoxia/Ischemia
   - Drug toxicity
   - Infection-fever
   - Metabolic abnormalities
   - Renal/hepatic dysfunctions
   - Surgical injury

Clinical Presentation and Diagnosis

Most seizures that occur in an ICU setting manifest as focal or generalized tonic-clonic convulsions (GTCS). By far, the most common seizure type is GTCS (including secondary generalization), with some reports observing approximately 90% GTCS as the presenting seizure type (1,2). These data suggest that seizure diagnosis is rarely a diagnostic dilemma, even in the ICU. Although uncommon, patients that present with complex-partial seizures (9%) or non-convulsive status epilepticus, may be difficult to diagnose, especially with the host of other critical care issues and sedatives administered. It is this population of patients with either undiagnosed recurrent seizures or frank refractory status epilepticus, where the potential for irreversible neurological injury is high. More recently, some investigators have evidence to suggest that the incidence of non-convulsive seizures is alarmingly high upto 34% of Neuro-ICU patients, and it is only for a lack of monitoring that these seizures are not detected (23). Therefore, it cannot be over-emphasized that EEG of ICU patients is crucial in settings where seizures may be a complicating feature of critical illness.

Treatment

Optimal treatment of seizures in the ICU, involves both the acute cessation of ictal activity and preventing recurrence, ideally by removing or correcting the physiological trigger and providing pharmacological prophylaxis against recurrence. Most commonly, seizures manifest as single episodes which serve to alert the care givers in dramatic fashion that a metabolic or structural abnormality exists.

For immediate treatment of seizures, benzodiazepines are considered the first line of treatment. They penetrate into brain rapidly, are potent GABA agonists, and serve to improve local inhibition of signal transmission. Commonly used benzodiazepines include diazepam, midazolam, or lorazepam. Each has a unique pharmacokinetic profile. Diazepam has been the popular standard, although its use against seizures is waning owing to the superior properties of the other two. Highly

lipophilic, diazepam rapidly redistributes away from the serum into fat. The result is that its effective anticonvulsant duration is on the order of only a few minutes, although its elimination time from the body is many hours and the longest of the three agents (24). Such kinetics could possibly result in brief seizure control yet a prolonged sedative effect if large dosages are required. Midazolam is also highly lipophilic and short acting, but is cleared by the liver much more rapidly than diazepam (>10x) resulting in better correlation between drug effect and clearance (25). Lorazepam, a compound with greater water solubility that prolongs its serum half-life, is clinically effective for several hours (26). In a recent randomized controlled trial with patients in status epilepticus, lorazepam was found to be superior than diazepam or phenytoin alone in terminating clinical and EEG seizures (26). Thus, it is reasonable to use lorazepam to the treatment of all GTCS in the ICU since rapid, maximal control is desired. In patients in whom prolonged sedation may seriously confound neurological management, initial treatment of seizures may be instituted with a short acting benzodiazepine to be followed immediately by a loading dose of phenytoin.

Once seizures are controlled, monotherapy with phenytoin for seizures is advocated to lessen the complications of drug interactions. Seizure recurrence should be managed first with acute treatment, again typically with benzodiazepines, followed by increasing serum concentrations of the primary anticonvulsant to high or maximal therapeutic levels. Should seizures become refractory, continuous EEG monitoring, intravenous phenytoin or inhalational anesthetics are recommended.

As alluded to earlier, it is important to realize that seizures occurring in the ICU setting may have unusual causes with complex features and treatments. Convulsions from theophylline toxicity carry a risk of morbidity and mortality that may exceed 40% (27) and part of the reason may be due to the fact that these seizures can be refractory to conventional anticonvulsant regimens (3). Repetitive seizures and status epilepticus may result. Hemoperfusion, dialysis, and activated charcoal all have their advocates for acute therapy, and some experts believe aggressive measures be initiated if theophylline serum levels reach 100 μg/ml (6,14,28). Isoniazid is another drug that requires non-conventional therapeutics. Due to its action as an antagonist to pyridoxal phosphate, treatment includes intravenous pyridoxine (3,29).

Treatment of other drug-induced seizures generally respond to benzodiazepines or barbiturates, and these should be considered first line options (7). Phenytoin is not particularly effective against most drug-induced convulsions, especially those triggered by B-lactam antibiotics. Hemodialysis may be a consideration if seizures are recurrent, particularly if renal failure complicates drug elimination.

Toxicity of Anticonvulsant Therapy

It must be kept in mind that there is no medical benefit without risk, and the initiation of anticonvulsant medications potentially introduces additional drug-induced side-effects to a critically ill patient. Both idiosyncratic and dose-dependent complications of therapy may occur and should be monitored for. Toxicity from anticonvulsants in ICU patients are predominantly a result of coexisting hepatic and renal dysfunction. Drugs such as phenytoin, carbamazepine, and valproic acid are heavily protein bound, and free serum drug is the active moiety. Therefore, in critical illness that alters serum protein levels, free drug concentrations may be severely increased even in the face of normal total serum drug concentrations. Routine monitoring of free drug levels is expensive, but warranted in such

patients. Hepatic dysfunction is less of a concern with phenobarbital (30).

The most common dose-dependent side-effects of anticonvulsants are sedation and mild cognitive impairment, even in therapeutic concentrations and particularly in the elderly and seriously ill. Ataxia and brainstem dysfunction may be a result of phenytoin or carbamazepine toxicity, while valproate induces tremors. Carbamazepine toxicity may present in biphasic fashion : acutely and subsequently as a consequence of increasing levels of the toxic intermediate 10-11 epoxide metabolise (30). Additional common acute, dose-dependent toxicities include transient leukopenia and thrombocytopenia (carbamazepine/valproate), megaloblastic anemia (phenytoin), and Syndrome of Inappropriate ADH Secretion–SIADH (carbamazepine).

Renal disease also may significantly perturb the clearance of anticonvulsants, although commonly only when the glomerular filtration rate falls below 10 mL/min (30). Phenobarbital and carbamazepine are not greatly affected, but phenytoin and valproate serum levels can rise or fall, and free levels in these cases may be a better guide due to the higher protein binding exhibited by these agents (30). During dialysis, phenytoin levels are not dramatically affected as is the case with phenobarbital. Other drugs may impede normal metabolism of anticonvulsants such as cimetidine, erythromycin, calcium channel blockers, coumadin sulfonamides, and amiodarone (30).

Idiosyncratic reactions of anticonvulsants may contribute to the morbidity of critical ill patients. Hypersensitivity is relatively common with agents such as phenytoin and carbamazepine with clinical features.of fever, rash and eosinophilia (31). Other drug effects that may occur (all are uncommon) include hepatic failure, pancreatitis (particularly valproate), agranulocytosis, aplastic anemia, Stevens-Johnson syndrome, and a Lupus-like syndrome (30). Severe hepatic dysfunction may rarely occur with valproate therepy secondary to a toxic metabolic intermediate. This potentially fatal action is best correlated in children under two years of age receiving polypharmacy for seizure control, and aspirin (32).

Prophylactic Therapy for Seizures

Patients in the ICU frequently suffer from a cerebral disturbance which carries a risk of seizures. Thus the issue is raised whether the benefit of seizure prevention outweighs its potential toxicity. As stated earlier, many seizures in the ICU are manifestations of transient metabolic or physiological abnormalities and the risk of recurrence is low if homeostasis is restored. For patients with physical pathology of the CNS, however, the risk of recurrence is frequently high.

Cerebrovascular accidents are a precipitating cause of seizures in 3-6% of patients (33, 34). Whether all stroke patients, as a group, should receive prophylactic anticonvulsant therapy has not been fully established. Hemorrhagic stroke carries a two-fold increase in the risk of seizures compared to ischemic infarction. Thus elderly patients, who are confused at the beginning and those who do have an early seizure (<1 week after stroke) have a high risk of recurrence and should therefore be considered for prophylactic therapy (34).

Patients with an intracranial tumor are at high risk for seizures, and are frequently prescribed prophylactic seizure medication. It is known for certain that patients with cerebral tumors, particularly gliomas, have a high recurrence rate of seizures. Once they occur, prophylactic therapy is mandated, although incompletely effective in more than 25% of cases (35). In case of head injury, as stated previously, the risk of seizures in early post-trauma period is approximately 4%. Offered appropriate

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treatment, reports suggest that the occurrence of a seizure does not influence the ultimate neurological recovery (36). Prophylaxis against seizures has not been demonstrated to prevent the possibility of epilepsy following recovery in a prospective cohort. However, the likelihood of further seizures and neurological deterioration does support aggressive treatment following an initial convulsion (22).

Personal Experience in the ICU

We followed up 52 cases of seizures who were admitted at different occasions in the ICU and following observations were made :–

1.	Metabolic abnormalities causing seizures	14
2.	Post anoxic	12
3.	Infections (Encephalitis, Meningites, Cereberal malaria)	09
4.	Primary Epilepsy	07
5.	Poisonings	05
6.	No cause could be found	05

Conclusion

Treatment of seizures in an ICU setting can be a challenging engagement. The difficulties of seizure diagnosis and treatment that present themselves when caring for critically ill patients can be daunting. The use of a variety of medications and intensive care management tend to lower, rather than elevate seizure threshold. The seizure may itself be subtle and require electrical confirmation, and the causative factor may be difficult to assign with confidence. Treatment of seizures is important, however, due to their potential for further neurological injury. Proper assessment of the risk for seizures in critically ill patients is also important, owing to the potential for anticonvulsant-induced toxicity. Decisions regarding prophylaxis are based on a toxicity/benefit analysis permitting a logical approach toward the prevention of seizures and optimizing neurological recovery in the ICU and during later recovery. Personal experience says that in an ICU setting one should always find out the cause like metabolic, infections, poisonings which if not searched may go undetected and poses a dangerous situation for the patient.

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