

Anti-epileptic prophylaxis following severe traumatic brain injury: A mini-review and UK-based audit within a military cohort.

ABSTRACT

Introduction

Traumatic brain injury increases the risk of both early and late seizures. Anti-epileptic prophylaxis reduces early seizures but their use beyond one week does not prevent the development of post traumatic epilepsy. Furthermore prolonged prophylaxis exposes patients to side effects of the drugs and has occupational implications. The American Academy of Neurology recommends that anti-epileptic prophylaxis should be started for patients with severe traumatic brain injury and discontinued after one week. An audit is presented here that investigates the use of prophylaxis in a cohort of military patients admitted to the UK Defence Medical Rehabilitation Centre.

Methods

Data were collected and analysed retrospectively from electronic and paper records between February 2009 and August 2012. The timing and duration of AED use and the incidence of seizures were recorded.

Results

During the study period 52 patients with severe traumatic brain injury were admitted to the rehabilitation centre: 25 patients (48%) were commenced on prophylaxis during the first week following injury whilst 27 (52%) did not receive prophylaxis. Only one patient (2%) received prophylaxis for the

recommended period of one week, 22 patients (42%) received prophylaxis for longer than one week with a mean duration of 6.2 months. Two patients (4%) had post traumatic epilepsy and started on treatment at DMRC.

Discussion

The use of anti-epileptic prophylaxis varies widely and is generally inconsistent with evidence-based guidance. This exposes some patients to a higher risk of early seizures and others to unnecessary use of anti-epileptics. Better implementation of prophylaxis is required.

INTRODUCTION

Traumatic brain injury within the British military

Patients with Traumatic Brain Injury (TBI) represent a significant proportion of complex cases treated at the Defence Medical Rehabilitation Centre (DMRC). Injuries may be sustained in both battle (blast injuries, ballistic wounds and fragmentation injuries) and non-battle incidents (road traffic collisions and assault). The most common mechanism for battle-related injury in current conflicts has been blast; this has been correlated with a tactical shift by the enemy towards use of improvised explosive devices (IED),[1]. IED blast-related TBI results in a higher ratio of closed to open injuries,[2,3], which is a significant difference from previous conflicts. In Vietnam and Korea, penetrating TBI was more common secondary to shrapnel and gunshot injuries respectively,[4,5]. Historically, mortality from TBI was high,[2] however, the different mechanism of injury, the advances in personal protective equipment and casualty care in current conflicts appears to have lead to an increased number of TBI survivors. In recent years, the rate of TBI has been increasing,[6] and a significant proportion of evacuated casualties have concurrent TBI,[2]. Therefore TBI is an increasing burden on facilities for acute care and rehabilitation within the Defence Medical Services.

Post traumatic epilepsy

It is well documented that TBI increases the risk of post traumatic epilepsy (PTE),[7-11]. The risk of first seizure is highest within the first year following TBI after which the risk drops substantially; however prolonged seizure free periods of up to 20 years have been reported,[7,10]. Seizures occurring within

one week after injury, termed early post traumatic seizures, reflect the acute insult suffered by the central nervous system and are not considered to be epileptic, unlike late seizures,[12]. Seizures experienced after one week, termed late seizures, occur after a period of epileptogenesis resulting in permanent changes to the brain's architecture and electrical activity,[13]. Epilepsy is defined by a history of at least one seizure in association with enduring disturbance of the brain that is capable of causing further seizures,[14]. In the context of severe traumatic brain injury a single seizure more than one week after injury would constitute a diagnosis of post traumatic epilepsy.

Pathophysiology of traumatic brain injury and epileptogenesis

Epileptogenesis is the neurobiological process that leads to development and progression of an epileptogenic focus capable of causing seizures,[13,21]. Maturation of an epileptogenic focus can take weeks or years and clinically corresponds to a latent period before the onset of seizures. Epileptogenesis is a complex molecular, intracellular and intercellular process that is not fully understood. Commonly proposed mechanisms can be organised into three overlapping responses: primary and secondary injury and the repair processes,[22-24].

Primary injury is the immediate effect during seconds and minutes after traumatic brain injury. Direct force of blast, blunt trauma or ballistics causes physical damage through compression and distraction of brain tissue,[24].

Secondary injury represents delayed non-mechanical pathophysiology causing further tissue damage,[22-24]. Traumatic impact results in a massive release of glutamate resulting in excitotoxic injury,[26,27], that corresponds to neuronal damage, glial swelling and cell death,[22-24]. There is disruption of glucose metabolism, free radical oxidative damage and mitochondrial dysfunction that compromise cell energy production and result in further cell death,[26,27] and cytotoxic oedema,[29]. Cell damage is compounded by concurrent impaired autoregulation of cerebral blood flow, vasospasm, and tissue ischaemia,[28]. There is macroscopic and microscopic vascular damage and breakdown of the blood-brain barrier,[25,26]. Resultant vasogenic cerebral oedema combined with cytotoxic oedema,[29-31] may lead to increased intracranial pressure and further compromise in cerebral blood flow,[30,31]. Initiation of inflammatory cascades and growth factor responses leads to reactive gliosis,[26] with eventual formation of a glial scar that can also encase foreign bodies.

Neural adaptive processes after TBI may contribute to functional recovery, however, they may also lead to epileptogenesis,[32]. Key processes include neurogenesis, axonal sprouting, axonal growth and angiogenesis,[22]. Axonal sprouting and establishment of new excitatory synapses results in the formation of recurrent excitatory synaptic circuits. Furthermore inhibitory GABAergic interneurons become atrophic and dysfunctional resulting in decreased inhibitory connectivity,[26,32,33]. These maladaptive processes generate foci potentially capable of generating seizure activity.

Consequences of early seizures

In the acute stages following injury, early seizures may further compound the initial cerebral injury,[34]. Seizure activity may exacerbate cell energy depletion at a time of energy debt with the potential for further cell death. A resultant increase in cytotoxic and vasogenic cerebral oedema would raise intracranial pressure, reduce cerebral blood flow and decrease tissue oxygenation. Early seizures increase the risk of the late seizures i.e. Post traumatic epilepsy,[11,15,16]. This may reflect the severity of injury in these patients or demonstrate an increased epileptogenic effect of early seizures. This may therefore have direct effect of patients' medical and functional outcomes. Furthermore the economic cost of early seizures may be unknown but could include prolonged ITU admission, further intensivist and neurosurgical procedures.

Current evidence and guidance standards for anti-epileptic drug prophylaxis after traumatic brain injury

The use of anti-epileptic drug (AED) prophylaxis in the first week after severe TBI reduces early post traumatic seizures,[34,35] and may prevent further neuronal injury. It was postulated that use of AED prophylaxis would hinder the process of epileptogenesis and prevent PTE. However Tempkin's review of studies showed that of prophylactic AEDs tested, none were effective beyond the first week in prevention of PTE following TBI,[34,35]. In keeping with this evidence the American Academy of Neurology (AAN) published guidance on the management of severe TBI and recommends the use of AED prophylaxis for the first week after injury but to discontinue after this

time,[35,36]. [There is a lack of data reporting current practice of AED prophylaxis after traumatic brain injury. This audit examines current practice of seizure prophylaxis after severe TBI, and how adherent this is to evidence based guidance.](#)

AUDIT OF ANTIEPILEPTIC DRUG PROPHYLAXIS

A cross sectional audit was conducted to establish the current pattern of AED use in patients with severe TBI admitted to DMRC. [This audit used the AAN guidance,\[36\] as the comparative standard. The](#) audit focused on these main areas:

1. The occurrence and timing of seizures
2. The administration of an AED within the first week
3. The cessation of AED prophylaxis at the end of one week
4. The duration of AED prophylaxis
5. The choice of anti-epileptic drug
6. The presence of a documented plan for the management of the prescribed AED

METHODS

All military personnel who sustained severe traumatic brain injury, as defined by the US Department of Defense criteria, admitted to DMRC between February 2009 and August 2012 were included in the audit. [The Audit was registered with the DMRC Audit committee, and all data collection and storage was held according to Caldicott guidelines.](#) Data were retrieved from the

Defence Medical Information Capability Programme, DMRC medical notes, copies of notes and referrals from referring hospitals. Data were collected including demographics, mechanism and severity of injury, incidence and timing of seizures, the timing and choice of AED prophylaxis, and the presence of a plan for subsequent AED use. [The duration of AED use was calculated from the date prophylactic AED was started to the date of medication cessation, including any weaning period. In accordance with published definitions, seizures less than one week after injury were reported as early seizures and those after one week were reported as late seizures.](#)

RESULTS

During the study 52 patients with severe traumatic brain injury were admitted to the rehabilitation centre. 26 patients were referred from Queen Elizabeth Hospital Birmingham (QEHB) and 26 from other UK hospitals. The mean age of patients was 29.1 years (median 26.8 years) and the follow up period ranged from 1-43 months with a mean period of 18 months (median 16.4 months). 21 patients had battle injuries and 31 had non combat related injuries; 21 had open TBI and 31 had closed TBI. Of the 52 patients: 14 had retained foreign bodies, 7 had single lobe contusion, 32 had multiple lobe contusions, 19 had subdural haemorrhage and 11 had diffuse axonal injury. [\(See Figure 1.\)](#)

1. From the cohort of 52 patients, 14 patients (26.9%) experienced one or more seizures: 12 patients had late seizures therefore fulfil criteria of post traumatic epilepsy (19.2%) and four patients had early seizures

(7.6%). Two patients had both early and late seizures (3.8%). Two patients experienced their first late seizure prior to admission to DMRC, two occurred during their admission at DMRC and eight occurred after discharge from DMRC. Of the 12 patients experiencing late seizures six (50%) were receiving AED prophylaxis, three (25%) had previously received and discontinued an AED, and three (25%) had never received AED prophylaxis.

2. Of the patients admitted with severe TBI, 25 (48%) were commenced on an AED for the first week after severe TBI (62% of patients referred from QEHB, 35% from other hospitals). Only one patient (2%) received AED prophylaxis for the recommended period of one week; 22 patients (88% of those prescribed an AED) received AED prophylaxis beyond the recommended timeframe; and two patients had on going treatment for PTE diagnosed in the acute hospital. [\(See Table 1.\)](#)

3. On admission to DMRC 21 (40%) patients were taking AED prophylaxis beyond the guidance period. Whilst at DMRC six patients (29% of patients on prophylactic AED) had their AED discontinued and a further five patients (24%) had AED prophylaxis weaned and discontinued after discharge. Eight patients (38%) remained on prophylactic AEDs for reasons including patient choice. At DMRC two patients experienced their first late seizure and started on appropriate AED treatment for PTE. [\(See Table 1.\)](#)

2.4. The mean duration of AED prophylaxis for patients with severe TBI was 6.2 months.

3.5. The choice drug varied for those 25 who were commenced on an AED, eight received more than one agent, with four having their AED switched to another and four receiving two or more AEDs concurrently. The most commonly used AED agents were Phenytoin (18; 72%), Levetiracetam (7; 28%), Carbamazepine (4; 16%) and Sodium Valproate (4; 16%).

4.6. Written plans regarding the management of prescribed an AED was provided for only one patient where an early or late seizure occurred. When AED prophylaxis was commenced and no seizures occurred, written advice was present for 10 / 15 cases (66.7%). However, advice to reduce and discontinue AED prophylaxis was recorded in only two patients (13%).

DISCUSSION

In recent conflicts the rate of TBI has been increasing,[6] and many casualties have concurrent TBI,[2]. However it is uncertain what the severity of these injuries is and the rate they are occurring within the UK military on and off operations. The risk of post traumatic epilepsy in the UK military is uncertain and work is ongoing in this area.

The risk of developing post traumatic epilepsy is variable dependent on type and severity of injury and other factors. The risk of developing PTE generally correlates with the severity of the injury,[7-9,15,16]. There is no universal agreement on traumatic brain injury scales, but most scales are based around the Glasgow Coma Scale (GCS). The US Department of Defense Traumatic Brain Injury scale is used within DMRC,[17]. Other independent risk factors include: Brain contusion especially when multiple and biparietal,[7,9], intraparenchymal haemorrhage,[4], subdural haematoma,[7,9], penetrating head injury particularly with retained metal fragments,[4,7,10], depressed skull fracture,[9], chronic neurological deficits,[4,15], loss of brain parenchyma,[4], early seizures,[11,15,16], and family history of idiopathic epilepsy,[8].

The incidence of PTE within the published literature varies significantly depending upon: definition of TBI, severity scales, entry criteria, population setting and duration of follow up. Direct comparison and meta-analysis is not possible due to this heterogeneity of study data. To contrast the background risk of epilepsy in the general population is between 0.05% - 0.09% per annum,[8,18].

From civilian studies: Annegers *et al*,[7] reported a cumulative incidence of PTE from a population of 4541 children and adults with mild, moderate and severe TBI as 0.7%, 1.2%, and 10.0% after five years and 2.1%, 4.2% and 16.7% after 30 years respectively. Ferguson *et al*,[19] report a higher incidence, from a population of 1173 adult and adolescents, over a shorter period of three years for mild, moderate and severe TBI as 4.4%, 7.6% and

13.6%. Englander *et al*,[9] report from a mixed cohort of 671 adults with moderate to severe TBI after two years at a similarly high level as Ferguson *et al*, as 13.8%. However, the large population based study of 78572 children and adults with TBI by Christensen *et al*,[8] reported results for mild TBI with an incidence of 1.2% after five years and 1.4% after 10 years and a significantly lower rate of PTE in severe TBI as 4.4% after five years and 5% after 10 years.

Examining the severity criteria of these studies and comparing them to those of the US DOD: The patients in the study by Annegers *et al*,[7] with severe injuries could be moderate by DOD criteria; in Englander *et al*,[9] patients would be moderate or severe; in Christensen patients could be classified as moderate by DOD criteria. Ferguson *et al*,[19] used the Abbreviated Injury Scale (AIS) of the head to classify TBI severity which is predominantly an anatomically based classification system which is not readily comparable, but may represent a greater severity compared to the other studies.

The risk of PTE is particularly high in battle-related TBI which is particularly related to the high proportions of penetrating injuries,[10]. From historical conflicts (Korea, the First and Second World Wars) the rate of PTE after five years was between 35-45%, [5]. From the Vietnam Head Injury study, the lifetime risk of PTE is 53% following penetrating TBI; this was after 35 years of follow up,[10]. The incidence of first seizure within 12 months was 25%, between 1-5 years 12.7% and between 10-15 years the rate was 4.1%, [10]. These figures are similar to those from Iranian casualties in the Iran–Iraq war

in which incidence of first seizure was 25.2% within 12 months and 9.8% between 1-4 years,[20].

In contrast to these historical conflicts more recently blast has been the most common battle-related mechanism of injury,[1], and blast-related TBI had been reported to cause higher ratios of closed injuries,[2,3]. Despite this there was still a high incidence open, particularly projectile, TBI within our population of personnel with severe brain injuries.

The rate of late seizures within our cohort of severe brain injuries of battle and non battle injuries was 23% over a mean follow up of 18 months. The mixed cohort is not easily compared to previous studies but this figure lies between previous reported rates from military and civilian environments. Within our population there was a high level of known [post traumatic seizure](#) risk factors [which may account for the relatively high seizure rate: In the battle injury group there was a high proportion of projectile injury by fragmentation or gunshot causing open TBI with retained metallic foreign bodies \(66%\). Single and multiple contusions were common in both groups \(71 %, battle, 77% non battle\). The proportion of patients with subdural haemorrhage was higher in the non battle group \(48%\) compared the battle TBI group \(19%\), which may represent injury patterns associated with blunt trauma compared to projectile injury.](#)

Within our cohort the rate of post traumatic epilepsy was higher in battle-related TBI compared to non battle related TBI which is in keeping with previous studies. Associations were seen between known risk factors and late seizures especially retained foreign bodies (see Table 2), however these should be viewed with caution due to the small population size. These findings highlight the need for further research to establish the risk of PTE in battle related TBI from recent conflicts and non battle related injury.

The guidance on AED prophylaxis in severe TBI aims to limit damaging sequelae associated with early seizures. Prophylaxis has been shown to reduce early seizures but prolonged use of AED prophylaxis does not protect against the development of PTE and may inadvertently cause the patient harm.

This audit demonstrates that practice of anti-epileptic prophylaxis in referring hospitals is highly variable and is generally inconsistent with evidence based guidance. Furthermore there is a need to change current management to align with current guidelines. It appears that several patients with severe TBI may not be started on appropriate prophylaxis. If started many patients have continued anti epileptic medication after the guidance period of one week and remain on medication for prolonged periods. The choice of AED agent used is variable, however Phenytoin is the most common option.

A significant limitation of this study is the cross sectional design, a cohort method may have been beneficial but time constraints did not allow in this

instance. This is potentially an avenue for further study. There is a small number of military patients with severe TBI that are not able to be admitted for rehabilitation at DMRC, whom have not been included in this audit. These patients are admitted to other rehabilitation units specialising in the most severe head injuries and low awareness states. It is noted that the number of patients who received initial AED prophylaxis may have been underestimated due to incomplete receipt of documentation to DMRC particularly from medical services on operations.

Phenytoin had been the traditional choice, which is echoed by the findings of this audit, but other drugs such as Levetiracetam are appealing especially when in a military setting in which access to Phenytoin monitoring is limited. Phenytoin has several side effects, drug interactions including induction of cytochrome P450 and requires serum level monitoring. Levetiracetam is a non enzyme inducing well-tolerated AED that can be delivered intravenously or orally and does not require blood monitoring,[37]. The efficacy of Levetiracetam is comparable to that of Phenytoin in prevention of early post traumatic seizures after TBI,[38-40]. However cost benefit should be considered as administration of Levetiracetam is more expensive than Phenytoin even when taking in to account laboratory monitoring of Phenytoin levels using American cost analysis models,[41,42].

The cost implications for the medical service of prolonged AED prophylaxis may be relatively small, however this does not reflect the true human economic cost. The cost of complications and side effects of AEDs, whilst

beyond the scope of this paper and potentially unknown, may be significantly higher for some patients. Furthermore within the military there are occupational implications of continued AED prophylactic therapy including limitations on weapon handling, driving, employability and promotion. As such it is important that AEDs be implemented promptly and that they are stopped at one week.

CONCLUSION

This audit has shown that current practice of epileptic prophylaxis after severe traumatic brain injury is generally inconsistent with evidence based guidance. Guidance recommends seizure prophylaxis for one week only after injury. However, many patients are not started on prophylaxis and if started many patients remain on medication for prolonged periods. The following recommendations were made: A uniform approach for seizure prophylaxis after severe traumatic brain injury should be incorporated into Clinical Guidelines for Operations. Local guidelines should be used and disseminated to inform referring Neurosurgical centres to improve AED prophylaxis use.

Key points of recommendation of future practice include: All patients with a severe traumatic brain injury should be prescribed a one week course of prophylactic AED. Patients identified on AED prophylaxis outside of published guidance period of one week should be considered for withdrawal or reduction of this medication if appropriate. Preferred AED agents should be established. Referral and admission documents should clearly record the incidence of

seizures and detailed use of AED as either prophylaxis or for treatment of PTE.

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