Admission patterns and survival from Status Epilepticus in Critical Care in the United Kingdom: An analysis of the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme database

Running head: Admission and survival patterns of status epilepticus in critical care

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Abstract

Background: The factors influencing outcome after Critical Care Unit (CCU) for patients with **s**tatus epilepticus (SE) are poorly understood. We examined survival for these patients to establish (a) whether the risk of mortality has changed over time and (b) whether admission to different unit types affects mortality risk over and above other risk factors.

Methods: We analysed the Intensive Care National Audit & Research Centre (ICNARC) database and the Case Mix Programme Database (CMPD) (January 2001 - December 2016). Units were defined as neuro-CCU (NCCU), general CCUs with 24-hr neurological support (GCCU-N) or general CCU with limited neurological support (GCCU-L).

Results: There were 35,595 CCU cases of SE with a threefold increase over time (4,739 in 2001-2004 to 14,166 in 2013-2016). More recent admissions were older and were more often unsedated on admission. Mortality declined for all units though this was more marked for NCCUs (8·1% in 2001-2004 to 4.4% in 2013-2016 compared to 5.1% and 4.1% for GCCU-L). Acute hospital mortality was 2-3 times higher than CCU mortality although this has also declined with time. GCCU-L appeared to have lower mortality that NCCUs (OR 0.84, 95% CI 0.72, 0.98) but after post-hoc adjustment for case mix there were no differences. Older age and markers of morbidity of seriousness were all associated with increased mortality risk.

Conclusions: The number of patients admitted to CCU for SE is rising but critical care and acute hospital mortality is decreasing. Patients treated in NCCU have higher mortality but this is explicable by more severe underlying disease.

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Introduction and background

Most patients in the UK with life-threatening neurological conditions are treated on general critical care units (GCCUs), where specialist neurological support is limited. Treatment in a specialist Neurocritical Care Unit (NCCU) may improve outcomes[1] and reduce length of stay (LOS)[2,3] although this may be confounded by case mix[4]; we demonstrated improved survival for intracranial haemorrhage when treated in an NCCU[5].

Status epilepticus (SE) causes death or severe disability if untreated [6-8]. Its incidence is estimated between 4·6 [9] to 41 per 100,000 [10], most often 10 to 20 per 100,000 [11-16]; and has increased over recent decades [15].

Age-standardized mortality for all patients with SE using population-based studies varied from 1·79 per million to 1·89 per million between 1999 and 2010 [17]. Mean adjusted mortality rate was 2·4 per million in England and Wales with a decrease in deaths between 2001 and 2013[18]. Guidelines for managing SE have evolved with improved neuromonitoring and new antiepileptic drugs[19-21]. Recent studies show case fatality rates from 8·8% to 10·7% [9,15,22], and lower (3·5%) in those admitted with a primary diagnosis of generalized convulsive SE [22]; there are no data on CCU mortality rates.

We investigated patterns of admission and outcome for NCCUs and GCCUs in the United Kingdom over the last 15 years using the United Kingdom's Intensive Care National Audit & Research Centre (ICNARC) database for adult critical care [23]. We examined whether (a) the risk of mortality from SE changed over time and (b) whether admission to different unit types is associated with mortality risk.

Methods

Case Mix Programme Database

The Case Mix Programme (CMP) is the national clinical audit for adult critical care in England, Wales and Northern Ireland. The CMP Database (CMPD) contains pooled case mix, resource use and outcome data on consecutive admissions to both general and specialist CCUs. Reasons for admission to critical care are coded using the ICNARC Coding Method, specifically designed for this purpose. CMPD has been independently assessed to be of high quality,[24], although the database's quality for SE has not been specifically tested. Support for the collection and use

of patient identifiable data without consent has been obtained under Section 251 of the NHS Act 2006 (approval number PIAG 2–10(f)/2005).

Selection of patients

Data were extracted for admissions to CCUs between 1 January 2001 and 31 December 2016. Cases were identified where the primary reason for admission to critical care was 'status epilepticus or uncontrolled seizures'. Admissions following elective surgery with a surgical code for SE were excluded (predominantly from one quaternary centre performing epilepsy surgery).

Classification of units

CCUs were grouped into three categories. NCCU were defined as either specialised units treating neurological and neurosurgical cases or units in a neurosciences centre with specialised neurocritical care area within a combined unit. GCCUs were sub-divided in those with neuroscience support (GCCU-N), units with 7 or more full-time equivalent consultant neurologists based at the same trust, which we considered as the minimum number to provide around the clock neurology cover; and GCCUs with limited neuroscience support (GCCU-L).

Case mix

Data were extracted for age, gender, location prior to admission, admission type, Glasgow Coma Score (GCS), sedation status and acute severity of illness, assessed with the ICNARC Physiology Score [23] and APACHE II score [25]. Both scores encompass a weighting for acute physiology defined by derangement from the normal range for 12 physiological variables in the first 24 hours following admission to the CCU. APACHE II additionally weights for age and for severe conditions in the past medical history.

Outcome

Data were extracted for vital status at discharge (dead or alive) from the CCU and at the end of the acute hospital episode. Patients transferred from the original hospital to another acute hospital were followed up until final discharge.

Duration of care

Data were extracted for LOS in the CCU and in acute hospital as well as location post-discharge from the CCU and acute hospital.

Statistical analysis

Time trends were examined by grouping secular periods into 4 groups (2001-2004, 2005-2008, 2009-2012 and 2013-2016). Case mix, mortality and episode duration were described per time period for each category of CCU. Categorical data were summarised as number and percentage; continuous data as mean with standard deviation (SD) or median with interquartile range (IQR). Odds ratios for acute hospital mortality were calculated using multilevel logistic regression modelling, adjusting for age, gender, ICNARC Physiology Score, admission type, unit type and a linear time trend, with CCU as a random effect [26]. As a *post-hoc* analysis, to avoid residual confounding, the multilevel model was additionally adjusted for prior CCU admission (not for SE) during the same acute hospital stay, duration of acute hospital stay prior to CCU, admission (modelled as the logarithm of the number of days in hospital, truncated at 28 days due to skewness) and recording of a secondary reason for admission to the CCU and added to the descriptive tables. Patients transferred from another CCU and multiple admissions of the same patient within the same acute hospital stay were excluded from the multilevel models to ensure that each patient was included only once and that baseline data were from the start of the initial CCU episode. As a sensitivity analysis, the final multilevel model was repeated excluding patients with a CCU LOS of less than four calendar days to see if our findings were seen when restricted to the sub-group of more severely ill-patients. The analyses were performed using Stata 13.0 (Statacorp LP, TX, USA).

Results

Of 245 adult CCUs in England, Wales and Northern Ireland participating in the Case Mix Programme during the study period, we classified 25 as NCCU, 57 as GCCU-N and 163 as GCCU-L. Between 1 January 2001 and 31 December 2016, there were in total 1,669,462 admissions to these CCUs, of which, 36,011 (2·2%) had a primary reason for CCU admission of 'status epilepticus or uncontrolled seizures'; excluding 416 direct from theatre following elective epilepsy surgery, the final cohort for analysis consisted of 35,595 admissions.

Table 1 describes the demographics and case mix of admissions over time for NCCU, GCCU-N and GCCU-L, respectively. All unit types showed a marked increase in admissions, and more recent admissions are increasingly older. Patients in NCCUs were more likely to have transferred either from another hospital or had previously been an

in-patient, including a CCU patient for another reason. Whilst measures of case-mix were fairly similar across units and time, patients in GCCU-L were more likely to have been sedated for 24 hours or more.

Table 2 shows that critical care mortality was highest for patients admitted to a NCCU in the first epoch, declined over time across all unit types, but more markedly in the NCCUs where it was no greater than in other unit types in the last epoch. The CCU LOS was longer for NCCU patients, who were more likely to be transferred to a High Dependency Unit.

Acute hospital mortality was 2-3 times higher than critical care mortality. There was a similar reduction in acute hospital mortality with time although it remained highest in the NCCU patients. NCCU patients were more likely to be transferred to another acute hospital, presumably the source of initial referral.

After excluding 602 (1·7%) readmissions within the same hospital stay, 856 (2·4%) admissions transferred from another CCU (to avoid double counting) and 319 (0·9%) admissions with missing outcomes, 33,818 admissions were included in the multilevel logistic regression models (Table 3). Unadjusted acute hospital mortality was lowest for admissions to GCCU-L and highest for admissions to NCCU (OR for GCCU-L vs NCCU 0.84, 95% CI 0.72 to 0.98) with statistically significant heterogeneity across the three unit types (P = 0·038). Older age, worse ICNARC score on admission, admission from the same hospital, prior CCU admission, length of prior hospital stay and reason for admission were all associated with increased mortality risk. A more recent secular period was associated with reduced odds of mortality (3% decline per year, 95% CI 2 to 4%). After adjustment for potential confounders, acute hospital mortality remained highest in NCCU (GCCU-L: OR vs NCCU 0·85, 95% CI 0·73 to 0·98; GCCU-N: OR vs NCCU 0·82, 95% CI 0·69 to 0·96; P-value for heterogeneity = 0·037). Post hoc investigation identified that admissions to NCCUs tended to have longer prior stays in acute hospital, were more likely to have had a previous CCU admission (not for SE) and more likely to have a neurological secondary reason for admission. Adjustment for these additional confounders greatly reduced the variation in acute hospital mortality across different unit types (P value for heterogeneity=0·51), but the secular effect persisted.

The sensitivity analysis among 13,826 admissions with a CCU LOS of at least four days produced similar results.

Conclusions

Overall admission to the CCU

This analysis demonstrates an increase in the number of admissions over each period in every group of CCU which parallels the increased incidence of SE [15]. There has also been an increase of 4 to 5 years in the mean age of adult patients admitted to a CCU for SE. Further, in all groups of CCUs, an increasing proportion of patients were either not sedated in the first 24 hours on the CCU, or never sedated or paralysed. There was a tendency to a shorter LOS prior to CCU admission, particularly in the GCCU-L. In all units, patients were admitted with a progressively higher GCS, with similar changes in the ICNARC and APACHE data, which reflect general severity of illness. These data indicate patients are being admitted earlier and with less severe impairment of consciousness, for instance for monitoring of intravenous antiepileptic drug treatment rather than purely for sedation and ventilation, which is reflected in the increasing proportion of patients who are never sedated of paralysed. CCUs may be less selective and admit more patients at earlier stages of the condition, in addition to the probable overall increase in incidence [15]. This may indicate that emergency physicians are more aware of the importance of prompt intensive care treatment [7,20,21]. Nevertheless, patients with a prompt response to benzodiazepines in the Emergency Department would not typically be admitted to the ICU, so there is a bias towards more severe forms of SE in this cohort.

The excess of male admissions has remained consistent. This may reflect higher incidence of SE for men [27], possibly related to a higher prevalence of traumatic brain injury in males. It has been suggested that the in-hospital mortality in males is lower [14], but in our results gender did not predict mortality.

Specialist Unit admission

More patients were admitted to specialist NCCUs from within the same hospital, and more frequently came from Neurology and Neurosurgery, indicating the patients were already receiving specialist support, presumably because of the severity of their epilepsy or due to an underlying neurological disease. In the GCCU-L, patients were more likely to be admitted through the Emergency Department (ED), suggesting these cases develop SE de novo, or have been previously managed in the community. Thus, it is probable that patients in the NCCU have more severe forms of epilepsy or an underlying neurological disease.

There were increasing planned transfers to the specialist units, suggesting intensivists in general units increasingly refer SE to specialised units. Supporting this, specialist units in our sample had more recurrent admissions, consistent with a distinct case mix for NCCUs and GCCU-Ns of more patients with severe epilepsy who are more liable to develop recurrent SE and may include a larger proportion of cases whose prognosis is worse. The comparison of mortality will be influenced by this finding.

Mortality and outcomes

There was a low mortality rate in all types of CCUs. The high percentage of ventilated patients argues against it being due to a selection bias toward less unwell patients. The overall mortality data is comparable with other authors for SE in the literature [13,16,28,29,31]. This is an encouraging finding regarding the quality of CCU care for SE in the UK, however, the mortality rates in the literature vary significantly depending on the cohort and on whether ICU mortality, in-hospital mortality or 1 year mortality is taken, and overall comparisons are difficult. We were interested to note that overall mortality does not prove a benefit for NCCU versus GCCU-L admission. Whether or not specialist units per se confer a survival advantage, is a matter of ongoing debate, and a database would need to provide more information on the severity of illness to answer this question.

We are however concerned about the much higher acute hospital mortality than expected from the CCU mortality in this cohort, which is not restricted to the most severe forms of SE. This is similar to the pattern that we saw in a previous study [5]. Few patients are discharged from CCU in a terminal or palliative state and most deaths would be expected to take place either on the CCU, or after hospital discharge and featuring as 1 year mortality. We did not have cause of death so it is possible that these deaths are related to co-morbidity. Alternatively, it is possible that patients with recurrent SE may be refused readmission due to perceived futility. We consider that most patients with recurrent SE would re-admitted to CCU and death from epilepsy should be uncommon on general hospital wards. The results indicate that the quality of step down and ward care require further scrutiny. The excess mortality after discharge to the ward in our previous study also applied particularly to non-surgical neurological conditions (Guillain Barre Syndrome, Myasthenia Gravis) whereas for a "surgical" condition such as intracerebral haemorrhage or traumatic brain injury, despite comparable overall CCU mortality and severity, carry a much lower rate of deaths after stepdown [26]. Issues that may affect survival after stepdown from CCU include the expertise of ward staff in managing patients with aspiration risk, tracheotomy related complications, dysautonomia, reduced awareness, and the availability of specialist neurorehabilitation. These results raise the question of whether the pathways of step down in non-surgical patients increase risk of death. If so, there is an urgent need for better education of staff and introduction of protocol driven care for all neurological patients, comparable with trauma and stroke pathways. These data underline the importance of establishing the cause of death in patients who die in hospital after discharge from CCU, monitoring mortality rates, and questioning a perception of deaths as unavoidable.

A number of factors limit our conclusions. Firstly, this is a retrospective analysis of an intensive care database, and a prospective analysis using a case-control design would allow stronger comparisons between outcomes from different unit types. Furthermore, data from a general ICU database have limitations regarding specific diagnoses. We do not have access to the specific semiology of SE, which is important for estimating prognosis, and we do not have the exact cause of death. Furthermore, we do not know if our patients with SE had previous epilepsy and if so, the severity. The outcome for patients with known epilepsy who develop SE may differ from that in patients with general neurology or medical causes (including drug intoxication, encephalitis, trauma). We do not know the destination of all the patients after discharge from the CCU, and may be missing deaths of patients who are not readmitted to the CCU, although we believe the number is small. Also, we lack of data on the exact treatment used. Finally, we do not have precise information on the access of the contributing units to procedures such as continuous EEG. Our experience suggests that continuous EEG is available in a very limited number of units, and particularly 10 or more years ago will have been used in only a very limited number of cases.

However, even despite these limitations, important practical conclusion are possible. There are still significant differences in the practice and the provision of care for SE, despite better understanding of super-refractory SE and detailed management protocols,[8,21,30,31]. The outcome for patients with SE should continue to improve with increased recognition, early referral, better critical care, and better step down care.

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