A LOCAL STUDY ON THE INCIDENCE AND RISK FACTORS OF POST-TRAUMATIC SEIZURES AMONG PATIENTS WITH TRAUMATIC BRAIN INJURY

BY

DR CHAN KIN HUP

MBBS (Malaya)

UNIVERSITI SAINS MALAYSIA

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ABSTRAK

Pengenalan

Sawan adalah salah satu komplikasi yang serius akibat kecederaan kepada otak. Insiden and faktor-faktor risiko keadaan ini banyak, and didapati berbeza sedikit antara populasi yang telah dikaji. Terdapat hanya sedikit data mengenai keadaan ini di kalangan populasi Malaysia. Tujuan kajian ini adalah untuk menentukan insiden and faktor-faktor risiko untuk terjadinya sawan selepas kecederaan otak di kalangan masyarakat tempatan.

Bentuk Kajian

Kajian berbentuk 'prospective observational' yang dijalankan di Jabatan Neurosains Hospital Universiti Sains Malaysia, Kubang Kerian.

Kaedah

Sebanyak 157 orang pesakit dari semua golongan umur yang mengalami kecederaan otak telah dimasukkan dalam kajian dari Jun 2007 hingga Disember 2007, kemudian rawatan susulan sehingga 12 bulan, atau sehingga mati, atau sehingga mendapat sawan yang pertama. Pesakit juga dibahagi kepada kumpulan berisiko tinggi and kumpulan berisiko rendah untuk mendapat ubat phenytoin selama sama ada seminggu atau setahun (untuk golongan berisiko tinggi) and phenytoin sama ada untuk setahun atau tiada phenytoin (untuk golongan berisiko rendah). Statistik yang digunakan ialah 'Kaplan-Meier curves' and 'Cox proportional hazards regression'.

Keputusan

26 daripada 157 (16.6%) pesakit mengalami sawan selepas kecederaan kepala. Antara 26 ini, 11 (42.3%) mengalami sawan awal (kurang daripada 7 hari selepas kecederaan)

manakala 15 (57.7%) yang lain mendapat sawan antara 8 hari hingga 12 bulan selepas kecederaan (sawan lewat). Masa purata untuk mengalami sawan lewat adalah 9.4±3.2 bulan. Risiko mendapat sawan awal dan sawan lewat berbeza. Untuk sawan awal, risikonya adalah umur muda (p=0.021, 95% CI =0.806, 0.982) and pesakit yang terintubasi (p=0.029, 95% CI=1.194, 25.913). Untuk sawan lewat, risikonya adalah kecederaan otak yang teruk dimana 'Glasgow Coma Scale' antara 3-8 (p=0.036, 95% CI=1.065, 6.464). Ujian 'log-rank' untuk rawatan dengan phenytoin untuk golongan berisiko tinggi and berisiko rendah tidak bersignifikasi (statistik log-rank 0.31, p=0.5784 untuk golongan berisiko tinggi; statistik log-rank 0.23, p= 0.6283 untuk golongan berisiko rendah).

Kesimpulan

Insiden sawan selepas kecederaan otak di kalangan masyarakat tempatan adalah 16.6%. Faktor risiko untuk sawan awal adalah umur muda dan pesakit yang terintubasi, manakala faktor risiko untuk sawan lewat adalah kecederaan otak yang teruk. Phenytoin tidak efektif sebagai agen pencegah sawan selepas kecederaan otak.

ABSTRACT

A LOCAL STUDY ON THE INCIDENCE AND RISK FACTORS OF POST-TRAUMATIC SEIZURES AMONG PATIENTS WITH TRAUMATIC BRAIN INJURY

Introduction

Post-traumatic seizures are a well-known and serious complication of traumatic brain injury. The incidence and risk factors vary among study populations. Very little data has been published concerning this in the population of Malaysia. The aim of this study was to ascertain the incidence and risk factors for the development of post-traumatic seizures among patients with traumatic brain injury in this part of the country.

Design

This was a prospective observational study, carried out in Hospital Universiti Sains Malaysia, Kubang Kerian Kelantan under the Department of Neurosciences.

Method

A total of 157 patients from any age group who were diagnosed with traumatic brain injury were enrolled from June 2007 to December 2007, then followed up for 12 months, until death or their first post-traumatic seizure. Patients were further divided into high-risk and low-risk groups and randomized to receive either phenytoin for 1 week or 1 year (for the high-risk group) and either phenytoin for 1 year or no phenytoin (for the low-risk group). Survival analysis using Kaplan-Meier curves and Cox proportional hazards regression were used.

Findings

26 out of 157 (16.6%) patients developed post-traumatic seizures. 11 of the 26 (42.3%) developed early post-traumatic seizures (within 7 days) of the trauma whereas the remaining 15 (57.7%) developed seizures between 8 days to 12 months after trauma. The mean time to develop late post-traumatic seizures was 9.4±3.2 months. The risk factors for developing early and late post-traumatic seizures were different. For early post-traumatic seizures, the risk factors were young age (p=0.021, 95% CI =0.806, 0.982) and intubated patients (p=0.029, 95% CI=1.194, 25.913). For late post-traumatic seizures, the significant risk factor was severe head injury with a Glasgow Coma Scale of 3-8 (p=0.036, 95% CI=1.065, 6.464). Log-rank tests for phenytoin treatment in both high-risk and low-risk groups were insignificant (log-rank statistic of 0.31 with a p-value of 0.5784 for the high-risk group; log-rank statistic was 0.23 with a p-value of 0.6283 for the low-risk group).

Conclusions

Incidence of post-traumatic seizures in the local population was 16.6%. Risk factors for early post-traumatic seizures were young age and intubated patients; whereas for late post-traumatic seizures, only severity of head injury was found to be significant. Phenytoin was not beneficial as prophylaxis against post-traumatic seizures.

Key Words

Post-traumatic seizures, post-traumatic epilepsy, traumatic brain injury, head injury, incidence, risk factors, phenytoin.

A LOCAL STUDY ON THE INCIDENCE AND RISK FACTORS OF POST-TRAUMATIC SEIZURES AMONG PATIENTS WITH TRAUMATIC BRAIN INJURY

1. INTRODUCTION

Traumatic brain (TBI) injury poses a major health and socioeconomic problem throughout the world today (Maas *et al.*, 2008). One of the important, but poorly understood sequelae of TBI is post-traumatic seizures. Post-traumatic seizures can either be early (occurring within 1 week of the injury) or late (occurring after 1 week to years after the injury). Recurring late seizures make up the clinical syndrome of post-traumatic epilepsy (Pagni and Zenga, 2005, Black *et al.*, 1975, Englander *et al.*, 2003). The significance of an early post-traumatic seizure lies in the fact that a seizure attack within the acute stage may result in cerebral hypoxia, increased intracranial pressure and metabolic demand, an increased release of neurotransmitters, and thereby a higher incidence of mortality and morbidity due to secondary brain damage (Ates *et al.*, 2006, Vespa *et al.*, 2007).

The incidence of post traumatic seizures has been known to vary with the time period after injury and population age range under study, as well as the spectrum of severity of the inciting injuries, and has been reported to be anywhere from 4 to 53% (Pagni and

Zenga, 2005, Frey, 2003, Chiaretti *et al.*, 2000). It has been reported to be higher in children than in adults (Ates *et al.*, 2006).

Reported risk factors for the development of seizures in the first week after injury include acute intracerebral haematoma (especially subdural haematoma), younger age, increased injury severity and chronic alcoholism. Reported risk factors for developing late post traumatic epilepsy include loss of consciousness, amnesia lasting more than 24h, subdural haematoma, brain contusion, compound depressed fracture and early acute symptomatic seizures (Chiaretti *et al.*, 2000, Chadwick, 2000, Englander *et al.*, 2003, Frey, 2003).

Phenytoin is the drug most commonly prescribed for prophylaxis of early post traumatic seizures. Other agents that can be used include valproate and carbamazepine. However to date there is no evidence that treatment with such drugs reduces the occurrence of late seizures or has any effect on death and neurological disability. The use of newer antiepileptic drugs such as levetiracetam has yet to be studied (Chang *et al.*, 2003, Chadwick, 2000, Schierhout and Roberts, 1998).

2. LITERATURE REVIEW

2.1 EPIDEMIOLOGY

Traumatic brain injury is a major cause of morbidity and mortality worldwide with an ever rising trend. Severe head injury remains one of the leading causes of death and permanent disability in the young and productive age group in Malaysia, and causes a great burden and economic loss to both the family and country. The total number of road traffic accidents in Malaysia exceeded 223,000 in 1999 with an average of 16 deaths per day. In Hospital Universiti Sains Malaysia, a total of 522 cases of head injury was admitted to the Neurosurgical department in 1997, rising to 570 cases in 1999 (Kareem, 2003).

Epilepsy as a whole has a higher prevalence in Asia than in the developed world, with a median lifetime prevalence of 6 per 1000. From available literature, head injury is a leading causes of epilepsy in Asia. In one study, post-traumatic epilepsy accounted for 5% of total epilepsy and 20% of symptomatic epilepsy (Mac *et al.*, 2007). In military series, the incidence can reach 50% as these studies include patients with penetrating head injuries (Salazar *et al.*, 1985). Post-traumatic seizures can either be early (occurring within 1 week of the injury) or late (occurring after 1 week to years after the injury). A third category is immediate seizures (occurring <24 hours after injury)(Iudice and Murri, 2000, Chiaretti et al., 2000). Recurring late seizures make up the clinical syndrome of post-traumatic epilepsy (Pagni and Zenga, 2005, Black et al., 1975, Englander et al., 2003). The incidence of immediate seizures ranges from 1-4%, early seizures 4-25% and late seizures 9-42% (Agrawal *et al.*, 2006, Pagni and Zenga, 2006,

Haltiner *et al.*, 1997). In a large population based study by Annegers and colleagues involving 4541 patients over 49 years, it was found that the 5-year cumulative probability was 0.7% in patients with mild head injury, 1.2% in those with moderate head injury and 10.0% in severe head injury (Annegers *et al.*, 1980). It is estimated that 80% of individuals will experience their first seizure within the first 12 months post-injury and more than 90% by the end of the second year (Da Silva, 1990, (Englander *et al.*, 2003). The incidence of subclinical seizure activity is higher than that of overt seizures (Sarah, 2004). In up tot two-thirds of patients, late post-traumatic seizures are generalized, or focal with secondary generalization (Englander *et al.*, 2003, Haltiner *et al.*, 1997).

2.2 PATHOPHYSIOLOGY

Traumatic brain injury results in potentially epileptogenic brain damage through several mechanisms that may coexist in a single patient (D'Alessandro *et al.*, 1982). Immediate and early post-traumatic seizures are likely to have a different pathogenesis than late seizures. The mechanisms of epileptogenesis in early seizures are probably due to direct reactions to brain damage (Semah *et al.*, 1998, Annegers *et al.*, 1980).

Late seizures are thought to be due to cortical damage caused by free radicals generated following iron deposition from extravasated blood, and increased exitotoxicity due to accumulation of glutamate (Payan *et al.*, 1970). The pathophysiology of late post-traumatic seizures may also vary according to the type of injury. Closed head injuries produce diffuse axonal injury causing oedema and ischaemia leading to release of excitatory amino acids, cytokines, and other toxic mediators causing secondary cellular

damage (Graham, 1996). Penetrating brain injury produces a cicatrix in the cortex, while contusions and intracranial haemorrhages are associated with the toxic effects of haemoglobin breakdown products on neuronal function (Willmore, 1990). Following head injury or haemorrhagic cortical infarction, there is deposition of ferrous compounds in neural tissue, followed by a Haber-Weiss iron-catalysed reaction that results in the hyperproduction of hydroxyl radicals, triggering subsequent formation of peroxidative agents, peroxidation of phospholipids membranes and disruption of the cell wall leading to cell death (Rubin and Willmore, 1980). Iron liberated from haemoglobin and haemoglobin itself are associated with generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), both of which have been demonstrated to be involved in the mechanism of seizures induced by iron ions in the rat brain (Willmore *et al.*, 1978). Excessive activation of excitatory amino acid neurotransmitter receptors can generate free radicals which in turn are followed by release of more excitatory amino acids triggering excitotoxicity at these receptors and may be followed by formation of a chronic epileptogenic focus (Janjua *et al.*, 1990).

2.3 RISK FACTORS

The risk factors for developing both early and late post-traumatic seizures has also been studied in many case series. Annegers et al studied a population of 5984 head injured patients retrospectively in Olmsted County, Minnesota over a period of 49 years from 1935 to 1984. Significant risk factors for late seizures in this case were brain contusion with subdural haematoma, skull fracture, loss of consciousness or amnesia of 1 day or more and age over 65 years. In children less than 5 years, there was also increased risk

with linear skull fractures (Annegers, 2003). Englander followed 647 individuals prospectively and found the significant risks to be biparietal contusions, dural penetration, subdural haematomas, midline shift greater than 5mm and multiple intracranial operations. Early seizures were not studied (Englander et al., 2003). Guidice found post-traumatic epilepsy was not related to the presence or absence of intracranial heamatoma, but rather to the duration of coma (Guidice and Berchou, 1987). Early post-traumatic seizures could also be related to age, with Black reporting a higher incidence in patients in the 2-14 years age group (Black et al., 1975). Other risk factors reported include age more than 65, chronic alcoholism, base of skull fractures and intracranial operations (Frey, 2003, De Santis et al., 1979, Jacobi, 1992, (Temkin, 2003, Haltiner *et al.*, 1997).

2.4 ANTIEPILEPTIC DRUG PROPHYLAXIS

Numerous regimens and drugs have been studied and proposed in this respect, with some contrasting results. Temkin et al found that phenytoin and carbamazepine are effective in preventing early seizures, but not effective in preventing late seizures (Temkin et al., 1995). Pechadre et al treated 34 out of 86 severely head injured patients with a loading dose of intravenous phenytoin then followed by oral administration for at least 3 months. After 2 years follow-up there was a significant difference between the treated and untreated patients (Pechadre et al., 1991). Murri et al found that Phenobarbital at 1.5mg/kg/day had an efficient prophylactic effect against late post-traumatic seizures (Murri et al., 1980). Jacobi recommended prophylactic low dose Phenobarbital in children less than 5 years, and carbamazepine in children more than 5 years for at least 2

years for children at risk of developing post-traumatic epilepsy (Jacobi, 1992). Schierhout and Roberts did a systematic review of randomized controlled trials on post-traumatic seizure prophylaxis and concluded that prophylactic antiepileptic drugs are effective in reducing early seizures, but have no benefit against late seizures or death and neurological disability (Schierhout and Roberts, 1998). In 2003 the American Academy of Neurology published a practice parameter for the use of antiepileptic drugs prophylaxis in severe traumatic brain injury. The conclusions were that in adult patients with severe head injury, phenytoin prophylaxis is effective in decreasing the risk of early post-traumatic seizures. However, antiepileptic drug prophylaxis is probably not effective in decreasing late post-traumatic seizures (Chang et al., 2003).

3. RATIONALE

Although post-traumatic seizures is an important sequelae of TBI with potentially deleterious effects to life and recovery, to date there is very little data concerning incidence and risk factors among the local population. Ong and Dhillon found an incidence of 5.5% of early seizures in the paediatric population in General Hospital Kuala Lumpur (Ong *et al.*, 1996). The aim of this study is therefore to collect epidemiological data concerning post-traumatic seizures among the paediatric and adult population of patients who are admitted to Hospital Universiti Sains Malaysia (HUSM) for TBI and to elucidate factors that may contribute to the development of early and late post-traumatic seizures.

4. OBJECTIVES

The objectives of this study was

1. To obtain the incidence of post-traumatic seizures among the local population with mild, moderate and severe traumatic brain injury
2. To determine the relevant clinical and patient-related parameters that may contribute to the development of early and late post-traumatic seizures
3. To determine if treatment with antiepileptics is beneficial in the prevention of early and late post-traumatic seizures

5. RESEARCH METHODOLOGY

This was a prospective observational study, carried out in Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan under the Department of Neurosciences. The study was approved by local ethic committee with reference letter: USM/PPSP®/Ethics Com./2005 (146.4[1]). The study was conducted between June 2007 and November 2007.

Sample size was calculated using Power and Sample Size Program, downloaded from the Internet at www.mc.vanderbilt.edu/prevmed/ps/index.htm.

The parameters used for the high risk groups were $\alpha = 0.05$, power = 0.8, A = 12, F = 12, m = 1, $m_1 = 12$, R = 3. Sample size was 32 per arm, making 64 for both arms of the high risk group.

The parameters used for the high risk groups were $\alpha = 0.05$, power = 0.8, A = 12, F = 12, m = 1, $m_1 = 24$, R = 3. Sample size was 57 per arm, making 114 for both arms of the low risk group.

Total sample size estimation was 178.

Inclusion and exclusion criteria:

1. Inclusion criteria
    a. Patients from any age group with a diagnosis of traumatic brain injury admitted to the Neurosurgical Unit of HUSM
    b. Consent from patient or next of kin

2. Exclusion criteria

    a. Patients who were known epileptics

    b. Patients with prior history of head trauma

    c. Patients with severe ischaemic heart disease

    d. Patients with chronic renal failure

    e. Patients with uncontrolled diabetes and hypertension

    f. Patients with other serious medical problems that the researchers deem would adversely affect the results of the study

    g. Patients with such severe injuries who were not expected to survive 1 year

    h. Pregnant patients

    i. Patients with previous history of neurosurgical procedures

    j. Patients with other non-TBI neurologic diagnoses such as brain tumours, stroke, aneurysms, or diabetic coma

Main endpoints were :

1. Occurrence of a seizure
2. Death
3. Completed 12 months of follow-up

Traumatic brain injury was defined as injury from external causes resulting in either a transient or prolonged reduced conscious level, post traumatic amnesia, or abnormal findings on computed tomography (CT) of head.. All patients were treated by the standard protocol for management of head injured patients as practiced by the Emergency

and Neurosurgical Departments of HUSM (Appendix). The relevant clinical data for the patients on admission and their subsequent progress was charted on a proforma (as attached to the Appendix).

The computed tomography (CT) scan findings were taken as that reported by the admitting neurosurgical resident and confirmed by more senior lecturers later. The site or multiplicity of intracranial haematomas or contusions were not differentiated.

A baseline electroencephalogram (EEG) was scheduled for the patients during the course of the admission.

The occurrence of any surgical procedure was also collected for each patient. Surgical procedures were subdivided in craniotomies or craniectomies, insertion of intracranial pressure (ICP) monitoring device or extraventricular drainage (EVD) catheters and other non-neurosurgical procedures. For those who had more than one procedure, the more major procedure was the one included, for example if a patient had both a decompressive craniectomy and ICP monitor insertion, it would have been recorded under craniotomy/craniectomy.

Patients were further categorized to one of 3 groups : Those with immediate seizures (within 1 hour of the trauma), those at high risk of developing post-traumatic seizures and those at low risk for developing post-traumatic seizures. The criteria for categorizing the patients into the high risk group were presence of one or more of the following : 1. acute

subdural haematoma; 2. contusion>1cm in diameter; 3. penetrating brain injury and 4. depressed skull fracture more than 1 table thickness.

The patients who had developed immediate post-traumatic seizures were loaded with IV phenytoin 18mg/kg body weight over 30 minutes, then continued with a daily dose of phenytoin 300mg for adults and 5mg/kg body weight for children for 1 year. Those in the low risk groups were randomized to receive either phenytoin for 1 year or no phenytoin, with no loading. Those in the high risk group were loaded with phenytoin as above, and then randomized to either phenytoin for 1 week or phenytoin for 1 year. If any patient who was not on phenytoin developed a seizure at any point during the study period, he or she was then started on it.

Patients were monitored continuously during admission for any seizure activity, and on discharge, the patients and their caregivers were given information about the signs and symptoms of seizure activity. They were also given 3 monthly follow-up appointments at the Neurosurgical outpatient clinic in HUSM up to at least 1 year. Contact numbers were also obtained, and those who failed to attend clinic were contacted by telephone to ascertain presence or absence of seizure activity.

Data analysis was completed using SPSS version 12.1 by SPSS Inc. Chicago, IL. Significant value was set at p value less than 0.05.

6. RESULTS

6.1 DEMOGRAPHY OF THE STUDY POPULATION

6.1.1 Age

A total of 157 patients were recruited during the study period (from June 2007 to November 2007).

The age of the patients ranged from 2 to 87, with a mean age of 24.5±16.1 years. The majority of patients (42.7%) was in the 12 to 20 years age group. 83.4% of patients were aged 40 and below. The age distribution of the patients are illustrated in figures 5.1 and 5.2.

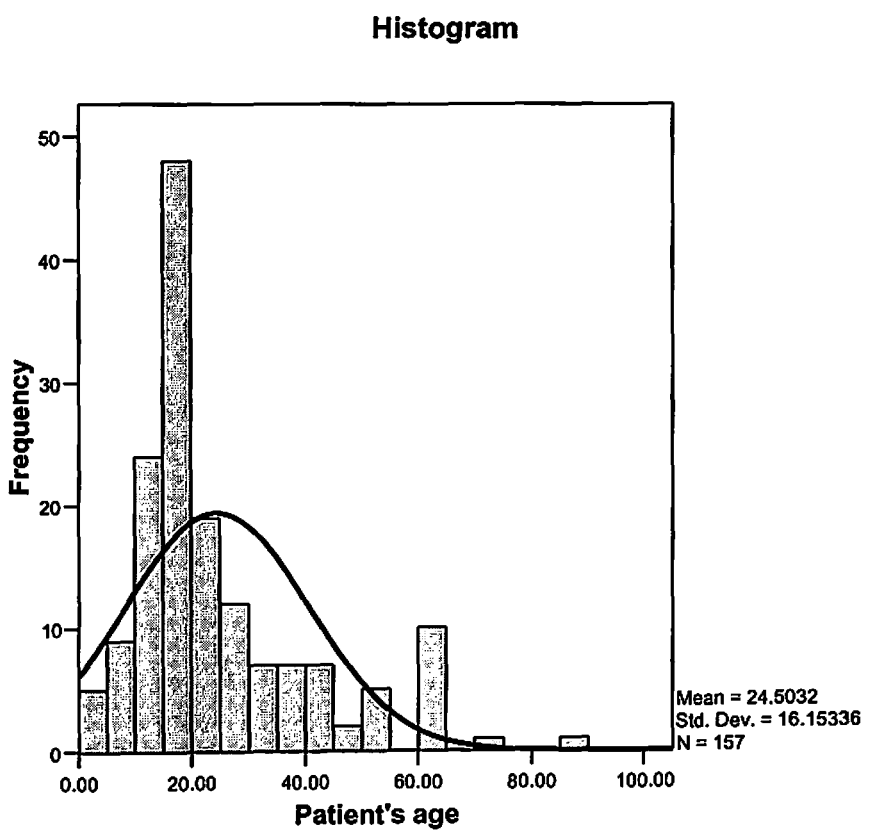

Fig 1 Distribution of patients by age

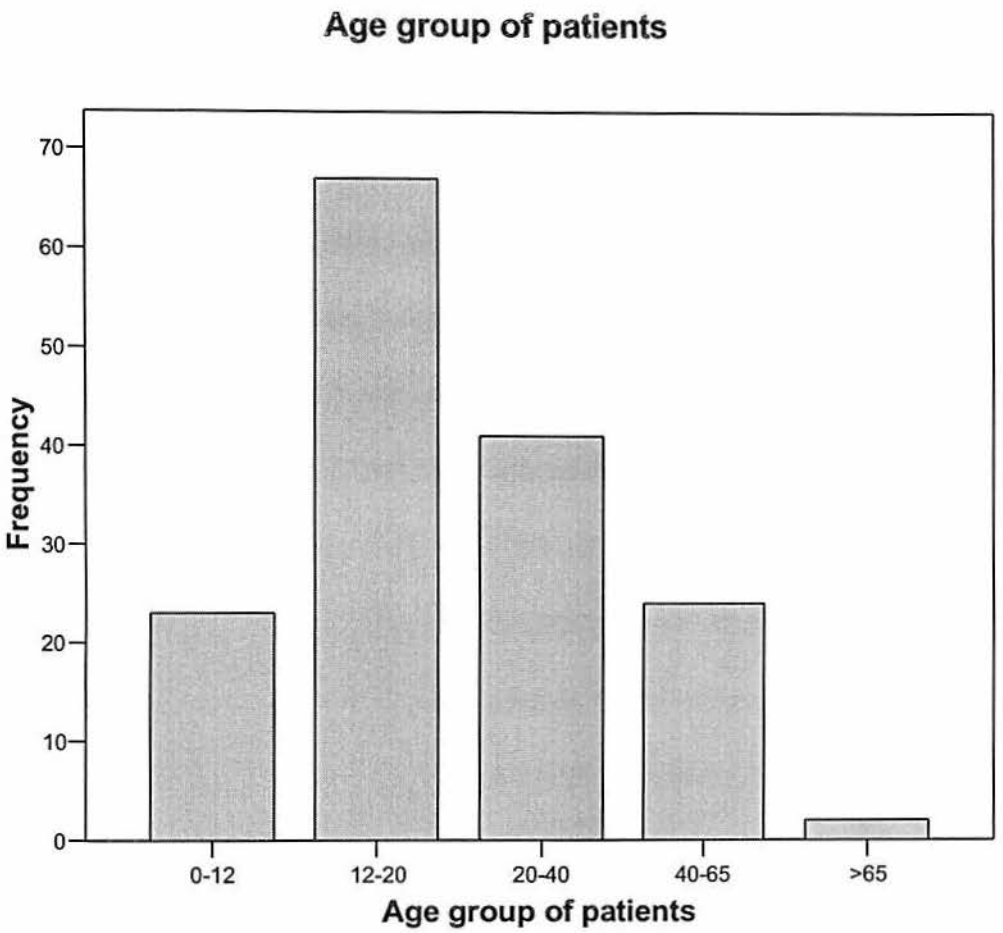

Fig 2 Distribution of patients by age group

6.1.2 Gender

Of the 157 patients in the study, 137 were male (87.3%) and 20 were female (12.7%).

The male to female ratio was 6.85:1.

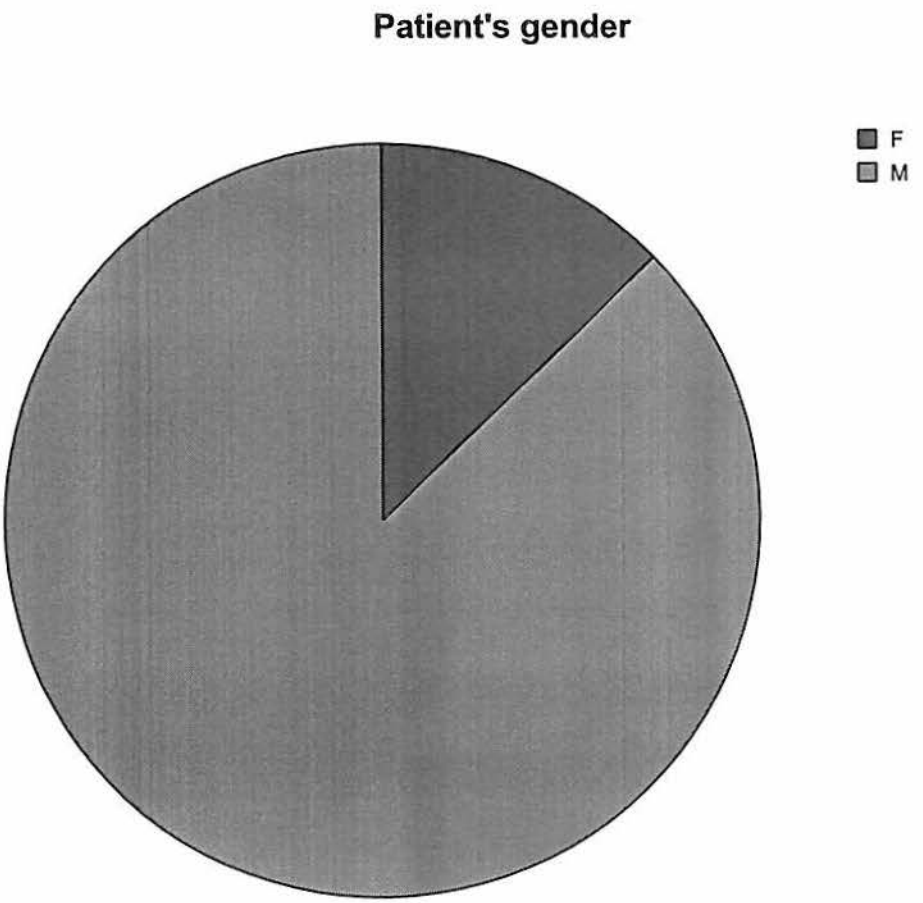

Fig 3 Distribution of patients by gender