UNIVERSITI SAINS MALAYSIA

TRAUMATIC BRAIN INJURY IN PAEDIATRIC MILD BLUNT HEAD TRAUMA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

By

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LIST OF ABBREVIATIONS

APEX	Accelerated Programme for Excellent
ASEAN	Association of South East Asian Nations
CATCH	Canadian Assessment of Tomography for Childhood Head Injury
CDC	Centre for Disease Control
CHALICE	Children’s Head Injury Algorithm for the Prediction of Important Clinical Events
CI	Confidence interval
CT	Computed Tomography
ED	Emergency Department
GCS	Glasgow coma scale
LOC	Loss of consciousness
HUSM	Hospital Universiti Sains Malaysia
LR	Likelihood ratio
MRI	Magnetic resonance imaging
NAT	Non-accidental trauma
PACS	Picture Archiving and Communication System
PECARN	Paediatric Emergency Care Applied Research Network

ROC	Receiver operating characteristic
SPSS	Statistical Packages for Social Sciences
TBI	Traumatic brain injury

ABSTRAK

Pengenalan: Kecederaan kepala ringan dalam kalangan pesakit pediatrik merupakan kes-kes yang kerap dirawat di Jabatan Kecemasan di seluruh dunia. Terdapat kontroversi berkenaan indikasi-indikasi untuk menjalani pemeriksaan imbasan tomografi berkomputer otak. Kajian ini bertujuan utama untuk mengenalpasti peramal-peramal klinikal untuk kecederaan otak dalam imbasan tomografi berkomputer. Kajian ini juga bertujuan untuk menentukan perkaitan antara muntah terpencil and muntah tidak terpencil dengan kecederaan otak dalam imbasan tomografi berkomputer.

Kaedah: Pesakit berumur bawah 18 tahun dengan kecederaan kepala ringan (GCS 13-15) yang datang ke Jabatan Kecemasan Hospital Universiti Sains Malaysia (USM) dalam tempoh tahun 2009 ke tahun 2013 dikaji secara retrospektif. Kami menilai pembolehubah klinikal termasuk mekanisme kecederaan, gejala-gejala dan tanda-tanda fizikal pada pemeriksaan fizikal untuk mengenalpasti peramal-peramal klinikal untuk kecederaan otak dalam imbasan tomografi berkomputer. Data yang diperolehi seterusnya dianalisa dengan ujian khi-kuasa dan analisis regresi pembolehuhah.

Keputusan: Sebanyak 274 kes telah dimasukkan dalam kajian kami. Purata umur dan sisihan piawai umur untuk pesakit kajian kami adalah 11.2 (5.39) tahun. Terdapat 49.3% pesakit didapati mengalami kecederaan otak dalam imbasan tomografi berkomputer. Kami telah mengenalpasti tiga peramal klinikal yang signifikan melalui analisis regresi pembolehuhah iaitu sakit kepala (adjusted OR 2.24, 95% CI 1.24, 4.05, p=0.008), pening kepala (adjusted OR 3.08, 95% CI 1.27, 7.51, p=0.013) dan hematoma pada kulit kepala (adjusted OR 2.93, 95% CI 1.60, 5.34, p<0.001). Kecederaan otak dalam imbasan tomografi didapati dalam 2 pesakit dengan muntah terpencil berbanding 71 pesakit dengan muntah tidak terpencil. Keputusan kajian ini telah mendapati terdapat hubungan yang signifikan antara muntah terpencil and muntah tidak terpencil dengan kecederaan otak dalam imbasan tomografi berkomputer (p<0.001).

Kesimpulan: Kajian ini telah mengenalpasti tiga peramal klinikal untuk kecederaan otak dalam imbasan tomografi berkomputer di kalangan pesakit bawah umur 18 tahun yang mengalami kecederaan kepala ringan di populasi kami. Imbasan tomografi berkomputer perlu dipertimbangkan secara serius untuk pesakit-pesakit yang muntah dan berserta dengan tanda-tanda lain yang mencadangkan kecederaan otak.

Kata Kunci: Pediatrik, kecederaan kepala, kecederaan traumatic otak, imbasan tomografi berkomputer

ABSTRACT

Background: Paediatric minor head injury is a common presentation in emergency department worldwide. There is controversy about which patients should undergo computed tomography (CT) of the brain. The purpose of our study was to identify the predictors for paediatric traumatic brain injury on CT scan in our population. We also aimed to determine the association between isolated versus non-isolated vomiting with traumatic brain injury on CT brain.

Methods: Children with minor head injury (GCS 13-15) presented to Hospital Universiti Sains Malaysia (USM) during the period from 2009 to 2013 were retrospectively reviewed. We evaluated clinical variables such as the mechanism of injury, presenting symptoms and physical signs on the examination for positive traumatic brain injury as determined by CT brain. The data was analysed by chi-square test, simple and multiple logistic regression analyses.

Results: A total of 274 patients were enrolled into our study. The mean and standard deviation age of study group was 11.2 (5.39) years old. Traumatic brain injury on CT scan occurred in 49.3% of patients. On multivariable analysis, we identified the following three predictors which were statistically significant: headache (adjusted OR 2.24, 95% CI 1.24, 4.05, p=0.008), giddiness (adjusted OR 3.08, 95% CI 1.27, 7.51, p=0.013) and presence of scalp hematoma (adjusted OR 2.93, 95% CI 1.60, 5.34, p<0.001). TBI on CT scan occurred in 2 of 24 patients in the isolated vomiting group versus 71 of 123 in the non-isolated vomiting group. We found significant association between isolated versus non-isolated vomiting with traumatic brain injury on CT brain (p<0.001).

Conclusions: Headache, giddiness and presence of scalp hematoma are independent predictors for minor blunt head injury in our pediatric population. CT brain should be seriously considered in children presenting with vomiting accompanied by other symptoms and signs suggestive of traumatic brain injury.

Key Words: Paediatric, head injury, traumatic brain injury, computed tomography

CHAPTER 1

INTRODUCTION

1.1 Background

Paediatric head injury is a common presenting complaint to an emergency department globally. In the United States, more than 600,000 children are presenting to emergency departments every year for examination and evaluation after sustaining head injuries (Langlois *et al.*, 2004). In year 2013, Centre for Disease Control (CDC) stated that in the United States alone, there were 473,947 visits to emergency department for traumatic brain injury by children aged 0 to 14 years, which is almost half a million (McKinlay and Hawley, 2013). A study by Langlois et al. in 2004 showed that traumatic brain injury accounts for approximately 500,000 emergency department visits, 37,000 hospitalizations and over 2000 deaths annually in the United States alone (Langlois *et al*., 2004). While in the United Kingdom, there are around 500,000 cases of head injuries reported among children each year (Homer & Kleinman, 1999). A recent review of incidence rate of traumatic brain injury for all age ranges, reported that Asia has the highest incidence rate of traumatic brain injury (McKinlay and Hawley, 2013). According to the Malaysian National Trauma Database 2009 report, blunt trauma made up of 96% of all injuries. Traumatic brain injury has become one of the leading cause of death and disabilities in children aged 1 to 18 years worldwide (del Demanio & delle Entrate, 2006).

Injury has always been the leading cause of death for children and teenagers in most of the developed countries such as United States and United Kingdom. Of these deaths, about 40 percent are the result of traumatic brain injury (Langlois *et al*., 2006). Overall mortality among children with traumatic brain injury who are treated in emergency department or require admission to hospital is 4.5 percent with the highest pediatric morbidity and mortality reported in children younger than four years of age

(Langlois *et al*., 2005). While in developed countries, traumatic brain injury has been reported as the most common cause of death and disability in childhood (Leurssen *et al*., 1988).

Most of the children are having full conscious level after minor head injury upon presentation and do not have any positive neurological findings when they first arrived at the emergency department (Munivenkatappa *et al*., 2013). Majority of them are sustaining minor blunt head injuries and mild depressed conscious level are fully recovered without neurological deficit or disabilities subsequently after been seen, observed and evaluated in the emergency department (Munivenkatappa *et al*., 2013).

Computed tomography scan of brain has always been recognized as the fastest diagnosing tools and the most reliable investigation of identifying an intracranial injury to prevent the evitable mortality and morbidity. However, the risk of ionizing malignancies associated with radiation exposure has always remained as a major clinical concern among treating clinicians. Therefore, computed tomography scan of brain should not be performed liberally and should be only used in selected patients when clinically indicated and justified.

In the current study, we determined the rate of traumatic brain injury on CT brain among paediatric minor head trauma with various associated symptoms and clinical signs. The findings from the current study will provide better clinical decision making and justification when deciding for CT brain imaging for the future paediatric patients who presented to ED Hospital USM after sustained a minor blunt head trauma.

1.2 Objectives

1.2.1 General objectives

- To evaluate traumatic brain injury on CT brain in paediatric minor blunt head trauma **<u>in Hospital USM.</u>**

1.2.2 Specific objectives

- To determine the association between isolated versus non-isolated vomiting with traumatic brain injury on CT brain in paediatric minor blunt head trauma **in Hospital USM.**

- To identify the associated factors of traumatic brain injury on CT brain in paediatric minor blunt head trauma **in Hospital USM.**

1.3 Research questions

1.3.1 Is there any association between isolated and non-isolated vomiting with traumatic brain injury in paediatric minor blunt head trauma **in Hospital USM**?

1.3.2 What are the associated factors of traumatic brain injury on CT brain in paediatric minor blunt head trauma **in Hospital USM**?

1.4 Research hypothesis

1.4.1 There is an association between isolated and non-isolated vomiting with traumatic brain injury in paediatric minor blunt head injury **in Hospital USM**.

1.4.2 Age, gender and mechanism of injury are the associated factors of traumatic brain injury in paediatric minor blunt head trauma **in Hospital USM**.

1.5 Operational Definitions

1.5.1 Paediatric

We defined a patient as a child or paediatric according to current legal definition used in Malaysia. The reference will be made to several existing statutes namely the Child Act 2001 and the Age of Majority Act 1971. According to both Child Act 2001 (Part 1) and the Age of Majority Act 1971 (Section 1), a child is defined as a person under the age of eighteen years old (Berhad, 2005). Therefore, the current study included all paediatric patients below eighteen years old and had fulfilled the inclusion criteria.

1.5.2 School legal age definition

The main legislation governing education in Malaysia is the Education Act 1996 (Act 550). According to Education Act 1996, a national school, national-type school or private school established shall provide a course of primary education design for a duration of six years but which may be completed within five to seven years. Every parent who is a Malaysian citizen residing in Malaysia shall ensure that if his child has attained the age of six years on the first day of January of the current school year that child is enrolled as a pupil in a primary school in that year and remains a pupil in a primary school for the duration of the compulsory education. Secondary education, on the other hand, lasts for five years, refers to as form 1 to form 5, will start as soon as the children completed their primary school education. Form 1 to form 3 is known as lower secondary education while form 4 and form 5 are known as upper secondary education. The Minister may provide for a transition class in any academic national secondary school (Act, 1996). Based on this Education Act, school age children are therefore defined as those children six years old and above in the current study.

1.5.3 Mild head trauma

Head trauma is defined as acute brain injury resulting from mechanical energy to the head from external physical forces (Teasdale *et al*., 1974) (Bressan *et al*., 2012). According to Teasdale et al, operational criteria for clinical identification of mild head trauma include the following:

(i) 1 or more of the following : confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours and/or other transient neurological abnormalities such as focal signs, seizure and intracranial lesion not requiring surgery

(ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation to the healthcare facility

1.5.4 Traumatic brain injury on CT scan (Dayan *et al.*, 2014)

Traumatic brain injury on CT scan was defined by any of the following descriptions:

- Intracranial haemorrhage or contusion
- Cerebral oedema
- Traumatic infarction
- Diffuse axonal injury
- Shearing injury
- Sigmoid sinus thrombosis
- Midline shift of intracranial contents or signs of brain herniation
- Diastases of the skull
- Pneumocephalus
- Skull fracture depressed by at least the width of the table of the skull

(Skull fractures were not regarded as traumatic brain injuries on CT unless the fracture was depressed by at least the width of the skull. Children with isolated non-depressed skull fractures typically do not need specific therapy or hospital admission)

CHAPTER 2

LITERATURE REVIEW

2.1 Pathophysiology of traumatic brain injury in minor head trauma

Traumatic brain injury that occurs after minor blunt head trauma is due to external force (rotational acceleration-deceleration) effect to the brain structures (Schutzman *et al*., 2014) resulting in either temporary or permanent impairment in brain function. This may or may not causing underlying structural changes in the brain matter or brain parenchyma (Schutzman *et al*., 2014). The patient must present with at least one or more of the physiological changes after traumatic head injury (Teasdale *et al*., 1974). Physiological changes refer to observed or self-reported loss of consciousness, amnesia and alteration in mental state or neuropsychological abnormality at the time of the injury (Teasdale *et al*., 1974). Anatomical changes can either present or absent in patient with head injury (Teasdale et al., 1974). These anatomical changes include various conditions such as scalp or facial wound or swelling, skull fracture or clinical signs of skull fracture, confirmed intracranial injuries such as brain parenchyma bleeding, injury to intracranial blood vessels, injury to the dura mater or intraventricular haemorrhage (Teasdale *et al*., 1974). The trauma mechanism generates a shearing force which can result in mechanical disruption of the neuron and causing the diffuse axonal injury subsequently (Teasdale *et al*., 1974). The different type of mechanical forces applied to the brain may determine the various natures of the resultant injuries (Schutzman *et al*., 2014). Acceleration force occurs when a moving object is striking on a stationary head. Linear acceleration is the least injurious force compared to other mechanical forces. Deceleration force, on the other hand, occurs when a moving head is striking on a stationary surface (Teasdale *et al*., 1974). Brain rotation occurs when the head is struck in an asymmetric manner. Combination of rotational and acceleration-deceleration forces could result in a widespread and serious intracranial injury

(Schutzman *et al.*, 2014).

2.2 Role of CT scans of the brain in TBI

CT scanning becomes the imaging modality of choice in many centres for TBI since few decades ago due to various advantages. The rapid imaging time, the widespread availability and the lower associated cost compared to other imaging modality such as magnetic resonance imaging (MRI) had made it as one of the important investigations while handling the cases of paediatric minor head trauma in emergency department daily. It is also relatively safe and has fewer absolute contraindications if compared to MRI (Mannix *et al*., 2012). The availability of CT scans of the brain hence provides a rapid and effective method for recognition and identification of children with TBI (Mannix *et al*., 2012). In fact, cranial CT scan is the reference standard for emergently diagnosing TBI in many hospitals worldwide. District hospitals without CT facility will refer those patients with suspected traumatic brain injury to tertiary centres for the purpose of CT brain imaging. CT imaging use among paediatric patients with head trauma had increased significantly during past several decades although recent work demonstrates modest decreases in cranial CT rates for children with blunt head injury. (Mannix *et al*., 2012). It is useful for detection of a clinically significant intracranial lesion, although certain small intra lesion lesions might not be clearly visible in CT scan (Mannix *et al*., 2012). It is particularly crucial especially when clinician are handling with certain timely critical and timely dependant intracranial lesions such as extra-dural or acute subdural hematoma as delayed surgery for children with these intracranial injuries is going to result in increasing morbidity and mortality rate (Baricolo *et al*., 1984) (Seelig *et al*., 1981). On top of that, CT scan also plays a paramount role in clinical prognostication and can be used a graphic evidence to aid the understanding of parents towards their children clinical condition after sustaining minor head injury (Baricolo *et al*, 1984). Children with mild head injury and concurrent brain lesions on CT scan have greater impairment on cognitive testing (Levin *et al.*, 2008). In term of decision for discharge, children with normal CT scan after minor head injury can be safely discharged home from emergency department and does not require routine hospitalisation or further observation in the emergency department as they are at very low risk for subsequent traumatic findings on neuroimaging (Holmes *et al*., 2011). Admission to hospital seemed to be unnecessary for them as this does not offer extra clinical benefit to patients (Holmes *et al*., 2011). This can reduce the length of stay in emergency department as well as length of stay in hospital. (Holmes *et al*., 2011).

Furthermore, failure of detecting a clinically significant intracranial lesion by not performing CT brain followed by improper disposition will subject the treating clinicians to subsequent unnecessary medico-legal liabilities such as medical negligence (Holmes *et al*., 2011) (Thiam *et al*., 2015).

2.3 Disadvantages and side effects of computed tomography scan of brain

The immediate benefits of CT brain and consequences of misdiagnosing even a single intracranial injury must be weighed against the side effects and disadvantages that may arise from the liberal use of this investigation (Munivenkatappa *et al*., 2013), . Munivenkatappa et al. recommended liberal use of CT brain as a reliable tool to rule out an intracranial lesion in a child with minor head injury (Munivenkatappa *et al*., 2013). However, performing cranial CT does expose children to ionising radiation and it increases the lifetime risk for radiation-associated malignancies (Brenner *et al*., 2001). A recent large retrospective study by Pearce et al. demonstrated an increase in the 10-year risk of both leukaemia and brain cancer for children who underwent a CT scan in childhood and young adulthood (Pearce et al., 2012). Brenner et al. reported that the rate of lethal malignancies from CT is between 1 in 1000 and 1 in 5000 paediatric cranial CT scans (Brenner & Hall, 2007). In view of that, exposure to ionising radiation remained as the main concern for both clinicians and parents of children (Palchak *et al.,* 2003). Furthermore, estimates of the incidence of TBI following head trauma from paediatric populations are relatively low (Palchak *et al.,* 2003). Kuppermann et al. reported that only 3 to 7 percent of children more than two years of age and older may have a TBI on CT scan after minor head injury while the incidence of TBI on CT brain for children younger than two years old was approximately 3 to 10 percent after minor head injury (Kuppermann *et al.,* 2009).

Similar incidence had been reported by Homer et al. as well in which less than 10 percent of children will have positive CT brain findings after sustaining minor head trauma (Homer *et al*., 1999) and only less than 1 percent children sustaining minor blunt head injury require neurosurgical intervention (Homer *et al.,* 1999). The drawback associated with increased radiation exposure countervails the merit of detecting a few extra clinical insignificant cases and the additional expenses spending on CT scan rendered the ‘all patients for CT brain’ strategy more costly and impractical compared to other more selective strategies (Homer *et al*., 1999).

Although CT brain is the test of choice for diagnosing children with head trauma, the procedure has many disadvantages that need to be considered other than radiation risk and lifetime risk of malignancy as mentioned above. Transferring a child to CT room for the purpose of the CT brain causing the child away from the direct supervision and observation of emergency physician and emergency medical officers. Most of the time, children are not cooperative with the procedure and often required pharmacological sedation while underwent CT of the brain and the risk and complications of performing procedural sedation such as respiratory depression and cardiac complication in children using potent sedative agent need to be considered seriously (Pena *et al*., 1999). Pena et al. had reported that the adverse event rate for procedural sedation and analgesia performed by pediatric emergency physicians was

2.3% (Pena *et al*., 1999). Various adverse events had been reported in her study which included oxygen desaturation less than 90% requiring intervention, paradoxical reactions, emesis, apnea and laryngospasm requiring bag-mask ventilation (Pena *et al*., 1999). In view of all these potential drawbacks, CT scans should ideally be selectively used when clinically indicated and justified.

2.4 Role of clinical decision rule in mild head injuries

To avoid unnecessary use of CT imaging in paediatric minor head injury, there are a few published clinical decision rules currently available to assist, guide and improve emergency physicians' decision making when handling cases of paediatric head injury to identify paediatric patients who are at low risk of sustaining traumatic brain injury after minor head trauma and obviate the need for unnecessary CT usage (Kuppermann *et al*., 2009) (Dunning *et al*., 2006) (Osmond *et al*., 2010).

Three recently published rules include a) Paediatric Emergency Care Applied Research Network (PECARN) rule, b) Canadian Assessment of Tomography for Childhood Head Injury (CATCH) and c) Children's Head Injury Algorithm for the Prediction of Important Clinical Events (CHALICE) (Kuppermann *et al*., 2009). Comparison among these clinical decision rules has been performed by Easter el al in one of the prospective cohort study, and it showed that CHALICE is the most specific rule among the three rules to identify clinically important traumatic brain injury. PECARN is being slightly more specific if compared with physician decision (Easter *et al*., 2014). CATCH rule, on the other hand, was neither sensitive nor specific if compared with other clinical decision rules (Easter *et al*., 2014). Variables included in each clinical decision rule are shown in Table 2.1. Although these clinical decision rules seemed to be helpful, advantageous and useful, there are still some limitations with these clinical rules. One of the existing problems for these clinical decision rules is that they had reported high sensitivity and acceptable specificity in their initial derivation cohorts, however, the subsequent validation study is either very limited or showed poor results if compared with the initial derivation study (Easter *et al*., 2014). The CHALICE rule, in particular had 87% specificity in a derivation cohort with a limited reference standard but poor specificity in the validation study (Easter *et al.*, 2014). Currently, the PECARN rule appears to possess the best specificity, but this may be because it has only been validated in a cohort from the same setting as the derivation cohort and not in a new setting (Easter *et al*., 2014).

Table 2.1 Decision rules for CT scan of brain in children with minor head injury

Variables	PECARN <2 years	PECARN >2 years	CHALICE	CATCH
History				
LOC	5 seconds or more	Any	>5 minutes	
Vomiting		Any	3 or more episodes	
Headache		Severe		Worsening
Acting abnormally to parents	Any			
Amnesia			>5 minutes	
Seizure			Any	
Concern for NAT			Any	
Severe mechanism †	Any	Any	Any	Any
Physical Examination				
Abnormal mental status	Any	Any	Drowsy	Irritable
Skull fracture	Any	Basilar	Penetrating, depressed or basilar	Open, depressed, or basilar
GCS score	<15	<15	<14	<15 at 2h
Neurological deficit			Any	
Scalp hematoma	Non-frontal		>5cm if <1 years old	Large, boggy

LOC, loss of consciousness; NAT, non-accidental trauma

†Severe mechanism was defined as the following:

For PECARN as motor vehicle crash with patient ejection, death of passenger, or rollover; pedestrian or cyclist without helmet struck by vehicle; fall greater than 0.9m if younger than 2 years and greater than 1.5 m if >2 years; or head struck by high-speed projectile;

For CHALICE as motor vehicle crash as occupant, pedestrian, or cyclist greater than 40 miles/hour; fall greater than 3 m; or head struck by high-speed projectile;
For CATCH as motor vehicle crash, fall greater than 0.9 m or 5 stairs, or unhelmeted bicycle fall.

2.5 Vomiting in mild traumatic brain injuries

Vomiting has been included in many clinical decision rules of traumatic brain injury in children such as PECARN and CHALICE (Kuppermann *et al*., 2009) (Dunning *et al*., 2006). History of post-traumatic vomiting is considered as one of the main significant indication to the request for CT brain in children presented to the emergency department after mild head trauma (Kuppermann *et al*., 2009). Few articles have reported vomiting as one of the common presenting complaint of children after a head trauma and it is an important predictors for positive traumatic brain injury (Nee et al., 1999). Nee et al reported that overall incidence of post-traumatic vomiting was 12% in children (Nee *et al*., 1999).

At the current stage, controversy still exists regarding the positive correlation between post-traumatic vomiting and intracranial injuries. Clear evidence to prove that post-traumatic vomiting is an independent predictor of the intracranial lesion is still lacking. Some articles have reported that post-traumatic vomiting may be a possible predictor of intracranial injury (Turedi *et al*., 2008). Turedi et al had reported that vomiting as a significant predicting factor for abnormal CT brain findings (Turedi *et al*., 2008). Kocyigit et al, on the other hand, found that vomiting as a significant factor for abnormal CT scanning and can be used as an indication for CT scanning in paediatric with minor head injury (Kocyigit *et al*., 2014). It has been suggested by Kocyigit et al. those neurologically intact children with full Glasgow Coma Scale (GCS) who demonstrate post-traumatic vomiting should be considered for CT imaging (Kocyigit et al., 2014).

2.6 Controversial issues regarding vomiting in mild traumatic brain injuries

Vomiting seems to be a significant predictor for traumatic brain injuries. However, there are few articles published in recent years have shown that a history of vomiting does not necessarily indicate that a patient is at high risk of clinically important traumatic brain injury, especially when the history of vomiting is present in the absence of other accompanying symptoms or signs suggestive of traumatic brain injury (Dayan *et al*., 2014). Some studies, in facts, revealed that vomiting as an insignificant factor for intracranial injury (Dunning et al., 2004) (Da Dalt et al., 2007). Post-traumatic vomiting is likely due to inertial forces (impulse) in its aetiology rather than contact forces (impact). Shearing forces are maximal in the brainstem whenever the head moves in the sagittal plane. This condition may lead to transient changes in the brainstem causing stimulation of the vomiting centre in the reticular formation of the lateral medulla (Aldman, 1986). A meta-analysis by Dunning et al, which reviewing