PURE MAXILLOFACIAL TRAUMA AND ITS CORRELATION WITH NEUROBEHAVIOURAL ALTERATION AMONGST MALAYSIAN: A LONGITUDINAL STUDY

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RESEARCH REPORT SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF CLINICAL DENTISTRY (ORAL AND MAXILLOFACIAL SURGERY)

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ORIGINAL LITERARY WORK DECLARATION

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Title of Research Report	: **Pure Maxillofacial Trauma And Its Correlation With Neurobeha-Vioural Alteration Amongst Malaysian:A Longitudinal Study**
Field of Study	: **Oral and Maxillofacial Surgery**

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ABSTRACT

Purpose of the Study: This research was performed to report the neurobehavioural alterations and brain microstructural changes in patients following pure maxillofacial trauma attending the Department of Emergency Medicine, University Malaya Medical Centre. The affiliation between the specific maxillofacial injury and its effect on the brain microstructural injury; and how the both former impacted the neurobehavioural deficits were investigated.

Material and Methods: A total of 16 subjects with maxillofacial trauma were included in this one-year logitudinal study. A pro-forma was developed to assist data collection. The data included demographic details, aetiology, clinical findings and radiograph investigations. All the subjects then underwent magnetic resonance imaging diffusion tensor imaging (MRI DTI), neurobehavioural assessment using Neurobehavioural Symptom Inventory (NSI) and The Hamilton Rating Scale for Depression (HAM-D) questionnaire. During the follow-up review, 6 subjects were able to complete the neurobehavioural assessment and only 4 completed both MRI DTI and neurobehavioural assessments. There were also 16 healthy subjects for control. Descriptive test was used to establish demographic data. Due to the initial and follow-up subject numbers discrepancy, non-parametric tests of Mann-Whitney U, Kruskal Wallis, Wilcoxon Signed Rank and Spearman's correlation tests were used in analysing intergroup and intra-group differences and correlation.

Results: The involved subjects were mainly male (n =12), adult (mean age 28.8 ± 6.45) with 11.94 ± 1.39 years of education. The maxillofacial injuries involved were soft tissue injury (n=4), and combination of soft and hard tissue injuries (n=12) with 82.9% fracture involving middle third area. There were non-significant difference in both NSI and HAM-D score in the initial and follow-up review. There were also no

significant relationship amongst initial and follow-up assessment in test group for the MRI DTI variables – fractional anisotropy (FA),axial diffusivity (AD), median diffusivity (MD) and radial diffusivity (RD).However, there were significant differences between control and test group.

Conclusions: The maxillofacial trauma injury had the possibility to cause microstructural brain changes and alter the behaviour presentation after the trauma event, though not significant.

ABSTRAK

Tujuan kajian: Kajian ini dijalankan untuk melaporkan perubahan *neurobevioural* dan mikrostruktur organ otak pada pesakit selepas kecederaan maksilofasial yang mendapatkan rawatan di Jabatan Kecemasan, Pusat Perubatan Universiti Malaya.Hubung kait antara kecederaan maksilofasial dan kesannya ke atas mikrostruktur organ otak beserta impak kedua-dua perkara tersebut ke atas perubahan *neurobehavioural* dikaji.

Kaedah dan Bahan: Seramai 16 peserta kecederaan trauma maksilofasial telah terlibat dalam kajian membujur selama setahun ini. Satu pro-forma telah dihasilkan bagi mengumpul maklumat berkaitan.Maklumat tersebut termasuk profil demografi, etiologi, carian klinikal dan pemeriksaan radiograf. Kesemua peserta melalui pengimejan resonan magnet *diffusion tensor imaging* (MRI DTI), pentaksiran *neurobehavioural* menggunakan *Neurobehavioural Symptom Inventory* (NSI) dan *The Hamilton Rating Scale for Depression* (HAM-D). Walau bagaimanapun bagi peringkat susulan, hanya 6 peserta yang menjalani pentaksiran *neurobehavioural* dan 4 peserta sahaja yang melengkapkan kesemua ujian MRI DTI dan penilaian *neurobehavioural.* Bagi tujuan perbandingan, seramai 16 peserta yang sihat juga telah disediakan. Analisis deskriptif telah dijalankan bagi melaporkan data demografi. Manakala, disebabkan oleh jurang antara bilangan peserta pada ujian awal dan susulan, ujian tak berparameter iaitu *Mann-Whitney U, Kruskal Wallis, Wilcoxon Signed Rank* dan *Spearman's correlation* dilaksanakan bagi analisa perbandingan dan hubung kait antara kumpulan peserta trauma dengan kumpulan sihat.

Keputusan: Secara keseluruhan, peserta kebanyakannya adalah lelaki (n=12), dewasa (purata umur 28.8 ± 6.45) dan mempunyai tempoh pendidikan selama 11.94 ± 1.39 tahun. Pecahan kecedeaan maksilofasial adalah kecederan tisu lembut sahaja (n=4)

dan gabungan tisu keras dan lembut (n=12) di mana 82.9% melibatkan fraktur di bahagian tengah 1/3 muka. Tiada perbezaan signifikan pada skor NSI dan HAM-D ketika ujian awal dan susulan.Ujian MRI DTI juga tidak menunjukkan perbezaan yang signifikan di dalam peserta trauma maksilofasial ketika penilaian awal dan susulan yang melibatkan pemboleh ubah tersebut - *fractional anisotropy* (FA), *axial diffusivity* (AD), *median diffusivity* (MD) *and radial diffusivity* (RD) Bagaimanapun, perbezaan signifikan dapat dilihat antara kumpulan peserta trauma dengan kumpulan sihat.

Kesimpulan: Kecederaan trauma maksilofasial mempunyai kemungkinan untuk menyebabkan perubahan pada mikrostruktur organ otak dan juga *neurobehavioural*, walaupun tidak signifikan.

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LIST OF SYMBOLS AND ABBREVIATIONS

AD	:	Axial diffusivity
AFNI	:	Analysis of functional neuroimages
DTI	:	Diffusion tensor imaging
FA	:	Fractional anisotropy
FOV	:	Field of view
GCS	:	Glasgow Coma Scale
HAM-D	:	The Hamilton Rating Scale for Depression
ICBM	:	International Consortium of Brain Mapping
MD	:	Mean diffusivity
MRI	:	Magnetic resonance imaging
mTBI	:	Mild traumatic brain injury
MVA	:	Motor vehicle accident
NSI	:	Neurobehavioural symptoms inventory
RD	:	Radial diffusivity
ROI	:	Region of interest
TR	:	Repetition time
TE	:	Excitation time
UMMC	:	University Malaya Medical Center

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CHAPTER 1: INTRODUCTION

1.1 Backgrounds

To date, the correlation between maxillofacial trauma and brain injury has not been fully understood (Tse et al., 2015). There were numerous literatures with contradicting opinions; some were in favour of protective mechanism of the facial skeleton inhibiting propagation of force to the brain (Chang et al., 1994; Stephens et al., 2016) and conflicting to that, there were postulations that believed the force towards facial skeleton could cause direct brain injury as well (Keenan et al., 1999; Martin Ii et al., 2002)

Motor vehicle accident (MVA) had been recognised as the most common cause of maxillofacial trauma (Pappachan & Alexander, 2012; Salentijn, Collin, et al., 2014) and approximately one third of the patients presenting with facial fractures have some form of intracranial injury (Hohlrieder et al., 2004). The high energy trauma linked to MVA (Brandt et al., 1991; Tse et al., 2015) directed towards the craniofacial skeleton can initiate damage to the brain tissue, as had been elaborated in previous studies (Isik et al., 2012; Veeramuthu et al., 2015) The main factors related to this damage include the trauma mechanism, direction of the impact and the amount of force transmitted or absorbed during the impact (L. Zhang et al., 2004; Assaf & Pasternak, 2008; Yan et al., 2013)

However, many believed the presence of brain injury were hidden in maxillofacial trauma patients whom did not present with related signs and symptoms at the initial phase of the trauma. The typical clinical course of absence of brain injury (i.e. no brain lesions found by CT scans) diagnosed in the emergency room is the clearing of confusion within 24 hour and patients being discharged afterwards (Levin & Diaz-Arrastia, 2015). These are largely attributed to lack of significant neuroimaging findings

in conventional CT and MRI imaging (Hughes et al., 2004; Silver et al., 2009). Thus, it is crucial for earlier recognition of associated brain injury to be made before the conditions worsen.

The relation between brain injury and behaviour deficit/outcome differs from individuals. Earlier literature stated the presence of psychological factors such as emotional distress, current life stress, medical problem, and chronic pain can resulted in long term behavioural and neurological complications after brain injury as compared to healthy subjects (Wäljas et al., 2015; van der Naalt et al., 2017) . Also, another study had suggested that a single concussion can result in lifelong impairment for some individual (Mayer et al., 2015). Recent studies had confirmed the hypothesis that some cognitive and behavioural disorders were detected not only in severe traumatic brain injury, but also in cases of mild traumatic brain injury, and even in cases of without head trauma (Nash et al., 2014). Thus, it is apparent that clinical examination, imaging and neurophyschological tests are complementary of each others to rule out brain injury.

Initial study in the neurophysiology of brain injury had shown that acceleration/deceleration forces and location of impact onto the facial skeleton to be an important factor (Hampson, 1995; Zwahlen et al., 2007) They found that the microscopic features were extensive diffuse degeneration of white matter that occurs in the midst of normal fibres and cortex (Levin & Diaz-Arrastia, 2015). This is of the interest of our study whereby we would want to investigate in details the possibility of microstructural changes in deep brain tissue in trauma patients. Their studies had influenced newer research in the role of deep brain processes and connectivity not only in neurological and psychiatric disorders ; movement disorders (Verlinden et al., 2016) and epilepsy (Gerrish et al., 2014) but also the post-traumatic cognitive alteration (Veeramuthu et al., 2016).

Only limited publications had been established on the incidence of maxillofacial trauma without brain injury and its link to neurobehavioural changes (Nash et al., 2014).Thus, it is apparent that clinical examination, imaging and neurophyschological tests are complementary to each others to rule out the presence of deep brain tissue injury. It is hoped that this study can initiate a better management protocol for patients following pure maxillofacial trauma to ensure optimum care and better treatment outcome.

1.2 Objectives of the study

1.2.1 Aim

The aim of this study is to investigate neurobehavioural alterations and brain microstructural changes in patients following pure maxillofacial trauma.

1.2.2 Objectives

I. To evaluate the brain microstructural changes in pure maxillofacial trauma subjects using diffusion tensor imaging (DTI) parameters.

II. To establish the relationship between the patterns of maxillofacial trauma, brain microstructural change and the neurobehavioral alterations.

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of motor vehicle accident and maxillofacial trauma

Malaysia is one of the countries in ASEAN (Association of The South East Asian Nations) with the population of more than 31 million. Based on a report in 2010, Malaysia had the highest rate of MVA amongst the ASEAN countries. On the same year, Malaysian Institute of Road Safety Research (MIROS) demonstrated there were 414,421 accidents with 28,269 casualties and 6,872 deaths (Nordin et al., 2015). The number has soared as reported by MIROS in 2016 whereby there were 7,152 deaths resulted from 521,466 accidents (MIROS, 2015).

Given its high number, MVA had contributed 5.8% of death amongst Malaysian population and was the fifth most common cause (Nordin et al., 2015) and is continuing to rise. Numerous studies reported the association of maxillofacial trauma case and MVA; MVA had caused 40% maxillofacial trauma in Tsang and Whitfield report (Tsang & Whitfield, 2012), 21.8% in Zelken et al. study (Zelken et al., 2014), and 39.5% in another report (Salentijn, Collin, et al., 2014).

The association of maxillofacial trauma with traumatic brain injury (TBI) had been elaborated widely in previous literatures. The most common injury is mild traumatic brain injury (mTBI) as stated that 76.9% of patients with brain injury were mTBI (Nordin et al., 2015) and about 80% of TBI cases in USA are classified as mTBI (Houseman et al., 2012)

Concurrently, the effect of maxillofacial trauma to the brain has undeniably elevated the cost of medical expenses (L. Zhang et al., 2004; Ramli et al., 2014). Patients affected were also reported to manifest trauma-related psychiatric changes either acutely or chronically (Mauri et al., 2014).Yet, the scarcity and paucity of studies in regards to

maxillofacial trauma and psychological distress; indirectly ensuing in the inability of clinicians to properly diagnose and treat the symptoms accordingly (S. Islam et al., 2012).

2.2 Human Skull and Brain

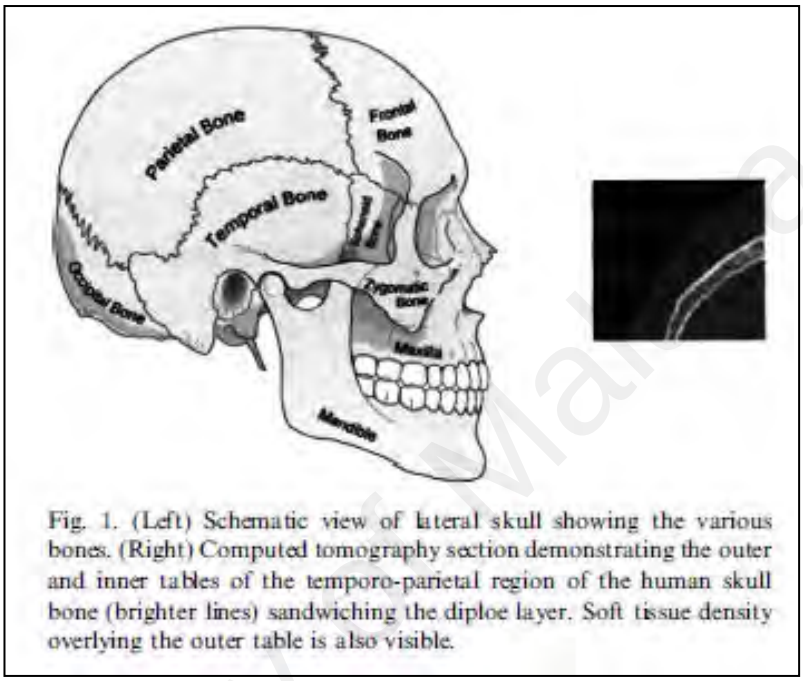

Fig. 1. (Left) Schematic view of lateral skull showing the various bones. (Right) Computed tomography section demonstrating the outer and inner tables of the temporo-parietal region of the human skull bone (brighter lines) sandwiching the diploe layer. Soft tissue density overlying the outer table is also visible.

Figure 2.1: Human Skull (Yoganandan & Pintar, 2004)

The human skull comprises of the cranium and the maxillofacial bones. The cranium bones are also known as neurocranium; which encircle and protect the brain from external damage. It can be divided to 2 parts:-

1. Calvarium
    - the vertex or the upper part
    - consists of frontal, occipital and parietal bones
2. Base of skull
    - The lowest part of the cranium
    - consists of temporal, ethmoid and sphenoid bones

The cranium bones are uniquely built up by 2 external and internal tables of cortical bones separated by cancellous bone; diploë. The internal bone is very sensitive to external trauma and may fracture even when the external table remains intact (Yoganandan & Pintar, 2004)

The maxillofacial bones are called as viscerocranium, as the name suggests they dwell sensory organs and viscera of the head. These include zygomatic, nasal, lacrimal, vomer, inferior conchae, maxilla, palatine and mandible bones.

These bones play major roles in daily activity and during trauma. The biomechanics of cranium and maxillofacial skeleton buttresses had been established in previous studies. It stated that all bones participated in the absorption of forced loads, transferring it from the fragile area to the robust one depending on the direction of the loads (Pappachan & Alexander, 2012). The buttresses are arranged 3-dimensionally:

1. Antero-posteriorly : Frontal, zygomatic,maxillary and mandibular.
2. Horizontally : Superior and inferior orbital rim, maxillary and mandibular alveolar rim, and inferior mandibular border.
3. Vertically : Nasomaxillary, zygomaticomaxillary, pterygomaxillary and posterior mandibular border.

Human brain consists of 3 sections;

1. The cerebrum
    - The largest part of the brain, known as forebrain.
    - Divided into frontal, temporal, parietal and occipital lobes, insula, thalamus, basal ganglia and hippocampus.

- Frontal lobes; executive functions (planning, social thinking), personality, emotional responses, some memory functions. It contains motor area.
- Parietal lobes; integration of sensory input (contains somatosensory and visual areas).
- Temporal lobes; memory, auditory functions
- Occipital lobes; visual processing

2. The brainstem
   - It extends from upper cervical spinal cord to the cerebrum diencephalon.
   - It is divided into the medulla oblongata, pons and midbrain.
   - It is the control centers for autonomic functions, as well as the circuits that control consciousness
3. The cerebellum
   - Situated posterior to the brainstem.
   - It is important in regulation of balance, movement and posture.

In this study, few white matter tracts of interest will be examined. White matter is located below the cortex layer which consists of neuron cell bodies. The white appearance is produced by the myelinated axonal fibres. White matter tracts connect both nearby and distal brain structures and can be distinguished according to the types of connections they mediate. Axons that contribute to similar destinations tend to form large bundles called white matter tracts. The anatomy of prominent tracts, which have a size as large as a few centimeters in the human brain, has been well-characterized in previous anatomical studies using postmortem samples (Y. Zhang et al., 2010).

1. Projection fibers connect structures over the longest distances in the cortical and subcortical grey matter (Lebby, 2013)

    - Corona radiata
    - internal capsule : anterior limb, posterior limb and genu
    - thalamic radiation :anterior,superior and posterior (includes optic radiation connecting lateral geniculate nucleus to the occipital lobe)
    - corticoefferent fiber : corticopontine tract (divided into frontal, temporal, occipitan and temporal lobe)

2. Association fibers connect different area of gray matter structures within the same hemisphere

    - Short fibre : connect within same lobe i.e U-shaped fibre
    - Long fibre : connect with different lobe i.e superior longitudinal fasciculus , inferior longitudinal fasciculus, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus
    - Fibre to limbic system i.e Cingulum (cingulated gyrus , parahippocampal), fornix and stria terminalis

3. Commissural fibers connect homologous structures in the left and right hemispheres and the largest fiber bundle

    - corpus callosum, anterior comissure,posterior comissure, and fornix

4. Brainstem tract – superior, middle and inferior cerebellar peduncle, corticospinal tract and medial lemiscus

The white matter tracks to be investigated include:

1. Middle cerebellar peduncle contains afferent fibres from the pontine nuclei

2. Corona radiata which is a pair of white matter tracts seen at the level of the lateral ventricles.
3. The internal capsule where a large number of motor and sensory fibers travel to and from the cortex. The anterior limb of the internal capsule separates the caudate nucleus and lenticular nucleus. The posterior limb separates the thalamus and lenticular nucleus.
4. Cingulum bundles of axon are fibres that surround superior surface of corpus callosum
5. Superior longitudinal fasiculus which is a bundle of long association fibers in the lateral portion of the medullary center of the cerebral hemisphere, connecting the frontal, occipital, and temporal lobes.
6. Optic radiation is a collection of axons from relay neurons in the lateral geniculate nucleus of the thalamus carrying visual information
7. Corpus callosum is a collection of white matter fibers that joins right and left cereberum hemispheres.

2.3 Maxillofacial trauma and brain injury

As in motor vehicle accidents, the victims are subjected to high velocity impact. If the impact exceeds the bone tolerance, the energy may be transmitted to adjacent structures through the fractured bones, which results in associated injuries such as brain injury (Pappachan & Alexander, 2012). The impact on the facial skeleton can be transmitted to the base of skull; the effect can range from transient loss of consciousness to more dangerous cereberal laceration (L. Zhang et al., 2004)

Regardless of varied opinions of maxillofacial trauma and brain injury, facial bones fracture should be considered as an indicator for increased risk of brain injury. During trauma, the head is exposed to mechanical changes including stress, strain, compression, tensile, torsion and displacement (Riggio & Wong, 2009). These mechanisms can cause

either contact or inertial impacts to the brain, and can be described into; focal lesions i.e. epidural hematomas, subdural subdural hematomas, contusions/intracerebral hematomas and diffuse lesions i.e. mild concussion, classic concussion and diffuse axonal injuries(Tsang & Whitfield, 2012).The direction of impact to the head and its related facial bone fracture has been described previously (Zwahlen et al., 2007) as;

1. Frontal impact causes Le Fort types I to III, nasoethmoidal, orbital floor and medial orbital wall , frontal sinus and median mandibular fractures, with or without condylar neck
2. Oblique impact causes zygomatic bone fractures (including those stated above), paramedian mandibular, with or without contralateral condylar neck and angular fractures
3. Lateral impact causes isolated zygomatic arch, with or without mandibular angular or condylar neck fractures of the same side.

An earlier study (Pappachan & Alexander, 2012) had stated that facial bone fracture occurs if the tolerance level of certain bone is exceeded as shown in Figure 2.2 . The highest tolerance level is borne by frontal bone at 200-400 G, and the lowest tolerance level is on the nasal bone with 30 G. Another literature (Hampson, 1995) had also presented with similar result whereby the frontal bone had the highest tolerance with 1000-7000 N and the lowest value was at the nasal area with 340-450 N.

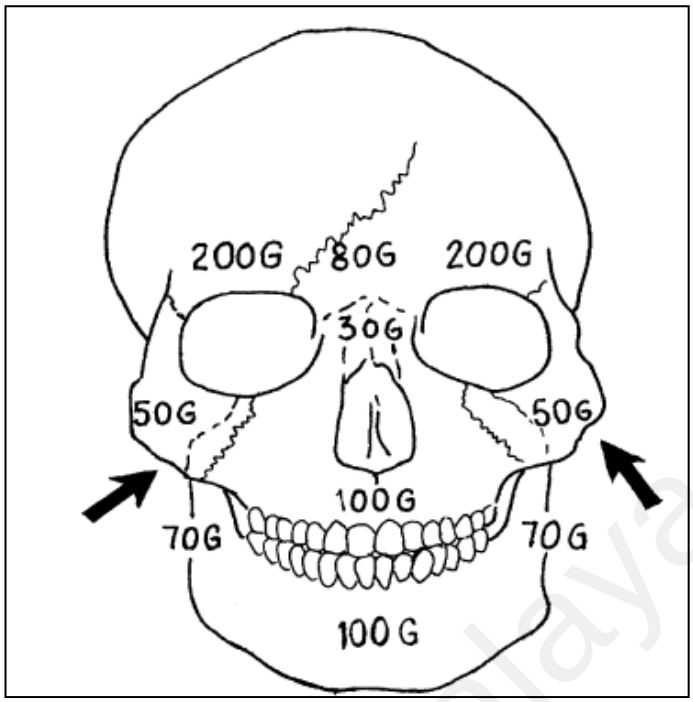

Figure 2.2: Facial bone in relation to degree of impact (Pappachan & Alexander, 2012)

In relation to that, a study was conducted in finite element head model to correlate facial injuries and brain injuries (Tse et al., 2015).They had discovered that frontal impact directed to the nose and lateral impact towards zygomaticomaxillary region causes the worst brain parameter derangement which is in line with the observation that facial bones adjacent to the brain results in higher risk of TBI.

To summarize, different direction of impact determined the severity and location of the facial bone fracture, which in turns influenced those of the traumatic brain injury pattern. Nevertheless, other factor such as the age of subjects, alcohol intake and the use of safety device may also influence.

2.4 Diffusion Tensor Imaging Finding In Maxillofacial Trauma

In conventional MRI or CT scan, subtle and slight changes of brain fibre pathways could not been visualised. This resulted in diagnosing brain injury based on clinical

presentations such as hypoglycaemia, vasovagal attack and mood disorders (Shenton et al., 2012; Veeramuthu et al., 2015). Diffusion tensor imaging (DTI) technology detects the structural integrity of neural tissue and neuronal tracts in the brain and spine via diffusion of proton sources movement in a certain direction when they are bounded such as water along the axis of white matter tracts (Cho et al., 2014). This has led to many clinical application in establish disorders such as multiple sclerosis, epilepsy, multiple sclerosis, Alzheimer disease, and traumatic brain injury (Lerner et al., 2014).

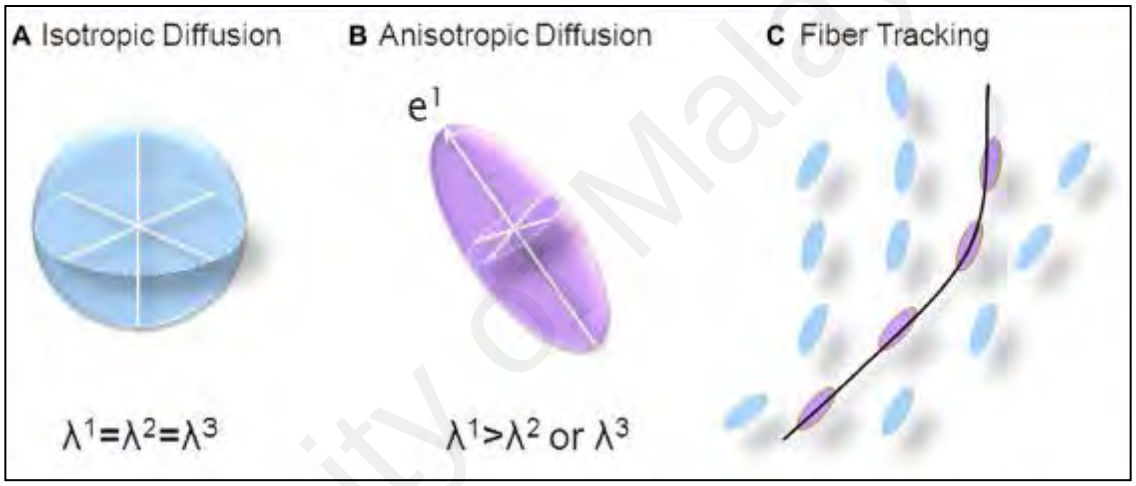

Figure 2.3: Diffusion tensor and fibre tracking image (Lerner et al., 2014)

A. Isotropic diffusion is produced when protons diffuse in unrestricted directions. It presents as spherical tensor and occurs in water and cerebrospinal fluid.
B. Anisotropic diffusion is produced when protons diffusion is restricted in some direction. It presents as ellipsoid tensor and occurs in white matter tract.
C. Fibre tracking is a post-production editing technique of the basic DTI data such as region of interest and TBSS.

In this study, parameters (Lerner et al., 2014) that were analysed for measurement include;

I. Fractional anisotropy (FA) calculated from the eigenvalues (ƛ) ranging from 0=complete isotropic and 1=complete anisotropic
II. Mean diffusivity (MD) is the average magnitude of proton diffusion regardless of the direction of movement.
III. Radial diffusivity (RD) reflects the diffusion of proton perpendicular to white matter tract.
IV. Axial diffusivity (AD) is the diffusion of proton longitudinal to the white matter tract

The use of MRI DTI in maxillofacial trauma is still at its infancy. To date, only one published report in this particular area. A study reported there were lower FA values in maxillofacial trauma subject as compared to healthy controls, showing an active pathogenic process. The involved tracts include anterior imb of internal capsule, cingulum, and corpus callosum. They had also noted that maxillofacial trauma without brain lesion had generally lower FA values across the time when compared to those with brain lesion (Veeramuthu et al., 2016).

CHAPTER 3: MATERIAL AND METHODS

3.1 Study design

This is an observational longitudinal study conducted involving maxillofacial trauma patient attending the Department of Emergency Medicine, University Malaya Medical Centre from April 2016 until April 2017.All the subjects were evaluated within 48-hour of the incident and repeated at 6-month interval.

3.1.1 Sample size justification

Sample size was estimated based on the aim of this study. The prevalence of patient with neurobehavioural disorder post maxillofacial trauma is the variable in this study. By taking z = 95% confidence (1 - a = 1.960) and 10% of margin error, the sample size justification were done using formula (Lwanga & Lemeshow, 1991) in such that;

Population prevalence, P = 29% (0.29) (Islam et al, 2010)

Power, z (1 – a) = 95% (1.96)

Margin error, d = 10%

$$n = z^{2}_{1-a/2} P (1 - P) / d^{2}$$

$$= 0.95^{2} (1.96)/2 \times 0.29(0.71) / 0.01$$

$$= 18$$

From the calculation, 18 numbers of subjects are needed to represent the population. For this study, we have managed to collect samples from 16 patients and 4 of them had

a set of complete 2-stage assessment. Nevertheless, the study will be carried on under the same manner in order to fulfil the data statistic requirement.

3.2 Study population

The subjects for this study were recruited from MVA victims who sustained maxillofacial trauma receiving treatment at the Accident and Emergency Department, University Malaya Medical Centre (UMMC), Kuala Lumpur. They were also being referred to the Oral and Maxillofacial Clinical Sciences Department for management of the injury involved. UMMC is one of the teaching hospitals located in Klang Valley under the Malaysian Ministry of Education .It is equipped with 1060 beds for in-patients facility and a total of 112,598 out-patients had received treatment at A&E in 2015 (UMMC Annual Report, 2015).

3.2.1 Inclusion and exclusion criteria

A total of 16 subjects who had fulfilled the following criteria were selected for this study as the test group. Another 16 normal subjects were set as control group.

(a) Inclusion criteria

i. Malaysian

ii. Age between 18 – 50 years old

iii. Mode of incident was MVA only

iv. Glasgow Coma Scale (GCS) upon arrival of 13 to 15

v. No other known pre-morbidity (e.g. no psychiatric disorders, hypertension, diabetes)

vi. Negative CT brain findings

(b) Exclusion criteria

i. Previous history of head trauma, known psychiatric disorders or central nervous system pathology

ii. Presence of drug usage

iii. Subjects with known non-MRI compatible

iv. Other major trauma that requires urgent surgical intervention under general anaesthesia

Informed consent was obtained from all subjects. The subjects underwent DTI procedure about 30 minutes per session within 24-48 hours post trauma followed by neurobehavioural assessment. Some subjects were admitted into the *Emergency Medicine Observational Unit* (EMOU) ward prior to the procedure to reduce the necessities for transportation and travelling to the hospital. A repeat DTI scan and neuropsychological evaluation were performed at 6 months of follow-up.

3.3 Diffusion tensor imaging MRI procedure

MRI-DTI procedure was conducted with a 3T MRI scanner (Signa HDxt; General Electric, Fairfield, CT) using an 8-channel head coil (Figure 3.1). The imaging protocol included;

i. Axial T1-weighted 3-dimensional fast spoiled gradient echo, repetition time (TR) 6.7 ms, excitation time (TE) 1.9 ms, field of view (FOV) 31 cm, matrix 256 x 256, slice thickness 1.2 mm, and slice overlap 0.6 mm, with an image scan time of 3 minutes and 48 seconds.

ii. Axial T2-weighted fast spin echo, TR 4240 ms, TE 102 ms, FOV 24 mm, matrix 512 x 384, thickness 5 mm, and spacing 1.5 mm, with image scan time of 2 minutes and 30 seconds.

iii. Coronal gradient echo, TR 655 ms, TE 20 ms, flip angle 15_, bandwidth 31.25, FOV 24 cm, matrix 320 x 256, thickness 5.0 mm, and spacing 1.5 mm, with an image scan time of 2 minutes and 7 seconds.

iv. The DTI sequence was obtained using these parameters: TR 13,000 ms, TE 81.2ms, FOV 24 cm, matrix 128 x 128, slice thickness 3.0 mm, 32 directions, diffusion weighted factor, b = 700 s/mm2, with an image scan time of 7 minutes and 22 seconds.

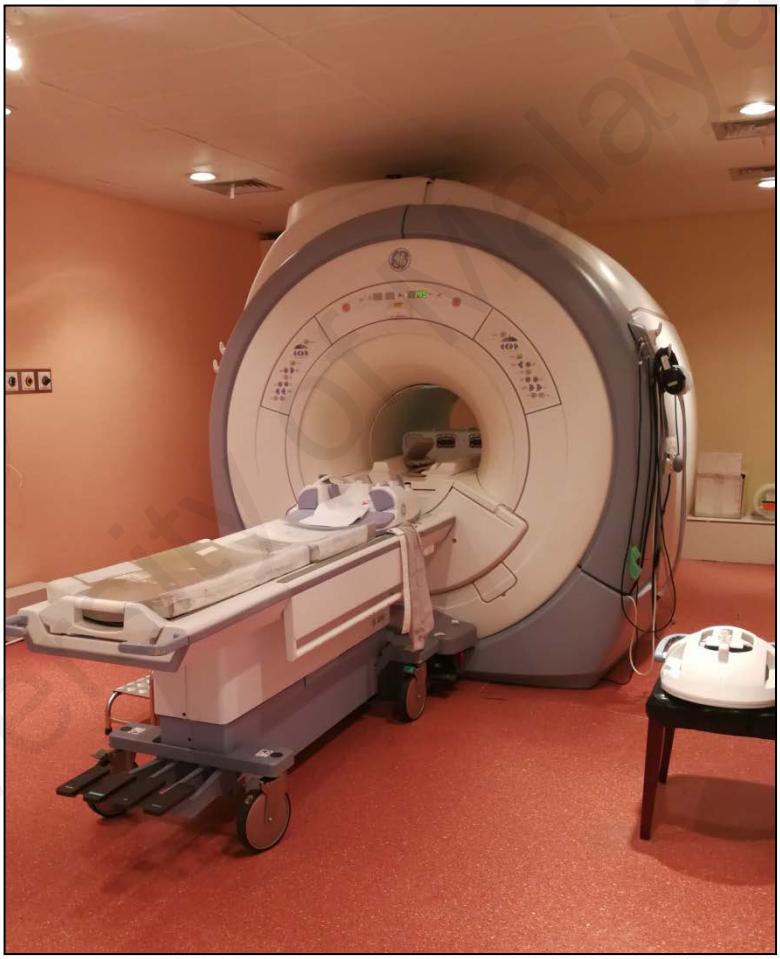

Figure 3.1: MRI scanner in the Biomedical Imaging Department, UMMC

3.4 DTI region of interest analysis

The DTI data went through stages of pre-processing, image registration, and analysis. The pre-processing was initiated with FSL version 5.0.6 (University of Oxford, Oxford, UK) was used for eddy current correction, skull stripping, and diffusion tensor fitting. The DTI images of each subject was registered to International Consortium of Brain Mapping (ICBM) DTI-81 atlas via DTI-TK version 2.3.1 (University of Pennsylvania, Philadelphia, PA)

The DTI analysis involved mapping of predefined regions of interest (ROI) and calculation of median FA, MD, RD and AD of each ROI using AFNI, version 2011_12_21_1014 (National Institute of Mental Health, Bethesda, MD. Subsets of 50 tracts of interest were adapted from the ICBM DTI-81 atlas:

i. Projection fibres
ii. Association fibres
iii. Brainstem tract
iv. Commissure fibres

3.5 Neurobehavioural assessment

The assessment conducted using Neurobehavioural Symptom Inventory (NSI) and The Hamilton Rating Scale for Depression (HAM-D). Both evaluations were done simultaneously within 2-week post trauma once the subjects had attained full GCS and emotionally also physically stable. The assessor had been validated with the supervisor prior to the commencement of the study.

NSI is also known as Post Mild TBI Symptoms Checklist (Wilde et al., 2010). It is a self-report questionnaire that measures the presence and severity of 22 common post-concussive symptoms regardless of pre-injury symptoms. The symptoms were then categorized into 5 cluster domains; vestibular, somatic, cognitive, affective and sensory which involved 20 symptoms and the other 2 as orphan domains as pictured in Table 3.1. The total score NSI is used to identify health symptoms and pertaining subjects can be referred for appropriate care.

Table 3.1: NSI and areas of neurobehavioural domain assessed

Symptoms	***Domain***
Feeling Dizzy	Vestibular
Loss of balance	Vestibular
Poor coordination, clumsy	Vestibular
Headache	Somatic
Nausea	Somatic
Vision problems, blurring, trouble seeing	Somatic
Sensitivity to light	Sensory
Hearing difficulty	Orphan
Sensitivity to noise	Sensory
Numbness or tingling on parts of body	Sensory
Change in taste and/or smell	Sensory
Loss of appetite or increased appetite	Orphan
Poor concentration, can't pay attention, easily distracted	Cognitive
Forgetfulness, can't remember things	Cognitive
Difficulty making decisions	Cognitive
Slowed thinking, difficulty getting organized, can't finish things	Cognitive
Fatigue, loss of energy, getting tired easily	Affective
Difficulty falling or staying asleep	Affective
Feeling anxious or tense	Affective
Feeling depressed or sad	Affective
Irritability, easily annoyed	Affective
Poor frustration tolerance, feeling easily overwhelmed by things	Affective

Each symptom was graded using Likert 5-scale from 0 to 4 to indicate the extent of each symptom within 2 weeks post trauma. The scale is as follows:

0	None	Rarely if ever present; not a problem at all
1	Mild	Occasionally present; it does not disrupt activities and can continue the activity and doesn't really cause any concern
2	Moderate	Often present; occasionally disrupts activities, can continue with some effort; and somewhat concerned.
3	Severe	Frequently present and disrupts activities; can only do thing that are fairly simple or take little effort; and feel needing help.
4	Very Severe	Almost always present; have been unable to perform activities and probably cannot function without help.

The Hamilton Rating Scale for Depression (HAM-D) is one of the widely used assessments for depression measurement in research and clinical practice (Kriston & von Wolff, 2011). HAM-D used in this study measures 17 symptoms of depression remains as the 'gold standard' for measuring depression (Rohan et al, 2016). There are extra four items to evaluate factors related to depression, such as paranoia or obsessional and compulsive symptoms. The symptoms are rated on a scale of 0–2 or 0–4 depending on each subset with a total score of 52, taken from the first 17 symptoms. The cut-off point for depression varies between different authors (Kriston & von Wolff, 2011). HAM-D and depression scale are shown in Table 3.2 and Table 3.3 respectively.

Table 3.2: The Hamilton Rating Scale for Depression (HAM-D)

Symptoms	*Score*
Depressed mood (sadness, hopeless,helpless,worthless)	0-4
Feelings of guilt	0-4
Suicidal	0-4
Insomnia early	0-2
Insomnia middle	0-2
Insomnia late	0-2
Work and activities	0-4
Psychomotor retardation	0-4
Agitation	0-4
Anxiety (psychological)	0-4
Anxiety (somatic)	0-4
Somatic symptom (gastrointestinal)	0-2
Somatic symptom (general)	0-2
Genital symptom	0-2
Hypochondriasis	0-4
Loss of weight	0-3
Insight	0-2
• Diurnal variation	
• Depersonalization and derealisation	
• Paranoid symptom	
• Paranoid and compulsive symptom	

Table 3.3: Cut-off point for depression

	Hamilton Rating Scale for Depression																								
	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	>31
Bech 1996		minor					less than major					major												severe	
APA 2000		mild						moderate					severe			very severe									
Furukawa 2007		mild										moderate												severe	
NICE 2009		subthreshold						mild				mode rate			severe										
Baer 2010		mild												moderate								severe			

3.6 Data collection

All subjects' data were collected using a standardized pro-forma pertaining to the demographic, trauma details, clinical presentation and diagnosis. They were recorded by single assessor as below;

(a) Patient demographic

The data includes age, race, gender and level of education. Age was grouped into 3 categories; i) 18-29 ii) 30-41 iii) 42-50. The subjects' race was divided into i) Malay, ii) Chinese, iv) Indian and iv) others. Level of education were classified into i) primary ii) secondary iii) diploma and iv) degree.

(b) Trauma details

Data includes date and time of injury; Glasgow Coma Scale (GCS); mechanism of injury; clinical findings, type of maxillofacial and associated injuries were recorded.GCS at the injury scene and time elapsed for the subject to achieve full GCS were retrieved from medical record. Episodes of loss of consciousness and retrograde amnesia were also noted. Mechanism of motor vehicle accidents (MVA) were divided into; i) Motorcycle vs motorcycle, ii) Motorcycle vs car, iii) Car vs car iv) Motorcycle skidded and vi) Others. Type of maxillofacial injuries included soft and hard tissues; classified according to regional anatomical landmark.

Table 3.4: Types of maxillofacial injuries

Anatomical region	Hard tissue injury	Soft tissue injury
Upper third face	Frontal bone fracture • Anterior table • Posterior table • Anterior and posterior tables Superior orbital rim	Laceration Abrasion Contusion Haematoma
Middle third injury	Orbital wall • Medial • Lateral • Floor Zygomatic • Arch • body Nasal bone Maxillary wall • Anterior • Lateral • Medial Palatal bone	
Lower third injury	Mandible • Condyle • Coronoid • Ramus • Angle • Body • Parasymphisis • Symphisis	

3.7 Statistical analysis

All data analyses conducted using SPSS statistical software, version 23.0 (IBM, Armonk, NY). To report the demographic and trauma details, descriptive statistics were performed. Categorical data were reported as percentage and frequencies while continuous data as means ± standard deviation (SD).

The Kruskall-Wallis test was used to compare two median differences of the neurobehavioural assessment and type of maxillofacial injury because the sample size is small with n=16 for initial reading and n=6 for post 6-month assessment. The significant value was set at α=0.05 with 80% power of the study.

Besides that, measurement for the relationship between maxillofacial trauma in test and control group with WM changes overtime, was executed using the Mann-Whitney test. The significant value was set at α=0.05 with 80% power of the study.

The intra-group comparisons for WM changes during initial and post-op were analysed using non parametric test, Wilcoxon Signed Rank Test in order to determine the difference significant between acute and chronic events among test group. The significant value was set at α=0.05 with 80% power of the study.

Lastly, Spearman's bivariate correlation was adopted to examine the association between neurobehavioural assessment and MRI DTI parameters over the two phases.

3.8 Ethical approval and funding

This study had received approval by the Medical Ethic Committee of Faculty of Dentistry, University of Malaya [Reference number: DF OS1621/0067(P)]. The funding of this study is supported by Postgraduate Research Scheme Grant, University of Malaya [Reference number: PPPC/C1-2016/DGJ/01].

CHAPTER 4: RESULTS

4.1 Demographic data

Of the 16 subjects who met the inclusion criterias, only 12 subjects had undergone the initial evaluation of MRI-DTI and neurobehaviourial assessment; and only 4 subjects fulfilled 2 assessment at initial and post 6-months review. 6 subjects able to attend both initial and follow-up review, however 2 were excluded because of inability to retrieve MRI-DTI image due to body movement (n=1) and presence of fixed appliance during post 6-months review which is contraindicated for MRI-DTI (n=1) test.

Table 4.1: Demographic data of population profile

Variables	***Mean ± standard deviation***
Age	28.8 ± 6.45
Education year	11.94 ± 1.39
Variables	***No of subject (percentage) n = 16***
Age category	
18-29	10 (62.5)
30-41	6 (37.5)
Gender	
Female	4 (25.0)
Male	12 (75.0)
Ethnicity	
Indian	3 (18.8)
Malay	10 (62.5)
Chinese	2 (12.5)
Other	1 (6.3)
Level of education	
High school	11 (68.8)
Diploma	5 (31.3)

The demographic details of subjects involved with maxillofacial trauma in this study were shown in Table 4.1.Subjects aged ranging from 18 to 41 years old and the mean age was 28.8 years old. Majority of subjects were 18-29 years of age (62.5%).

Higher predominance of male patients (75.0%) compared to female patients (25.0%) with Malay ethnicity represented majority of the case (62.5%). Most of the subjects' level of education were secondary level (68.8%) followed by diploma (31.3%).

4.2 Mechanism of injury

Table 4.2: Mechanism of injury

Variables	***Frequency (percentage)*** ***n*** *=16*
Motorcycle vs car	3 (18.8)
Motorcycle skidded	8 (50.0)
Others	5 (31.3)

As depicted in Table 4.2, the aetiologies of MVA in this study included skidded motorcycle which contributed to the highest percentage (50%), followed by collision between motorcycle and car (18.8%). Other mechanisms were cases of pedestrian with motorbike, collision of motorised vehicle with stationary object and skidded bicycle.

4.3 Maxillofacial trauma injury

In this study, 75% of subjects (n=12) sustained combination of soft and hard tissue injuries, while the other 25% (n=4) had soft tissue injury alone. The distribution of soft tissue injuries as depicted in Figure 4.1 included 50% laceration wound, 19% abrasion wound, 6% contusion and 25% mixed injury. The highest incidence of soft tissue injury involved mixed area (37%), then by the middle 1/3 region (31%), followed by 19% involving the lower 1/3 facial area and the least was 13% at the upper 1/3 area (Figure 4.2)

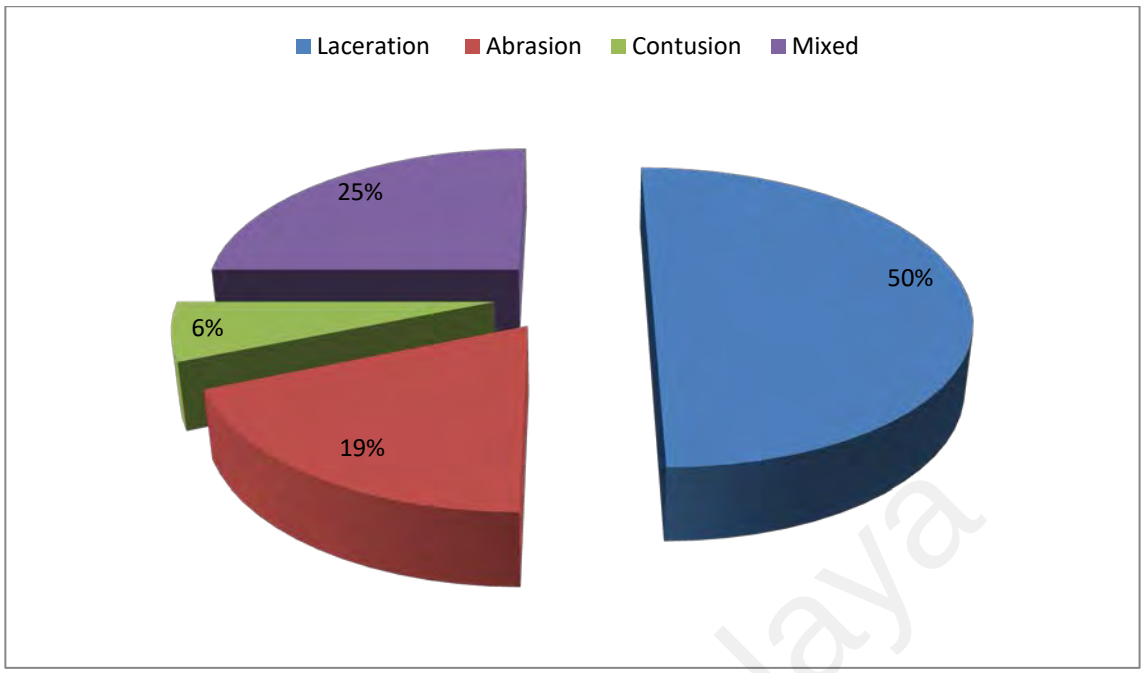

Figure 4.1: Type of soft tissue injury

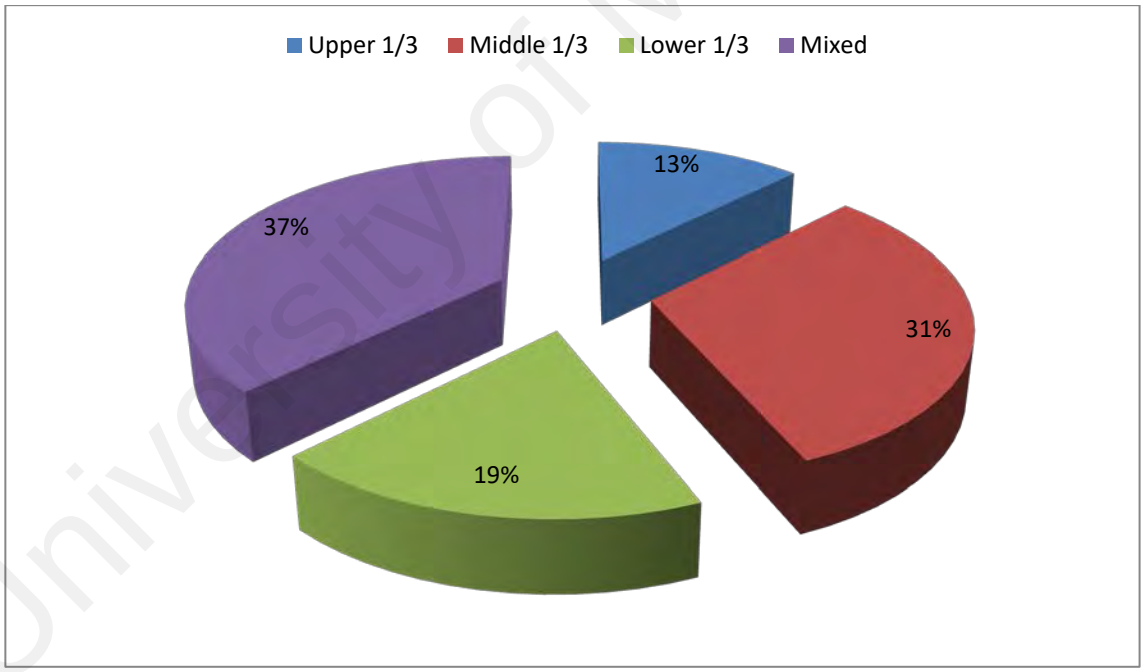

Figure 4.2: Location of soft tissue injury

There were a total of 41 maxillofacial fractures divided into 3 regions. The middle 1/3 facial fracture dominated the category with 82.9%. The most common site was maxillary wall fracture accounted for 29%, and then in descending order were zygoma fracture with 26%, orbit fracture (17%) and nasal bone fracture (9.8%). As for

mandibular, condyle was the most common site (7.3%) and one fracture each at ramus, body and symphisis. Fracture at the upper 1/3 facial area was the rarest – with single fracture at superior orbital rim.

Table 4.3: Distribution of maxillofacial fractures in relation to anatomical site

Region	***Anatomical site***	***Right***	***Left***	***Frequency (percentage)***
Upper third	Superior orbital rim	1		1 (2.43)
Middle third	Orbital wall			
	• Medial	1	1	2 (4.87)
	• Lateral	3	1	4 (9.76)
	• Floor		1	1 (2.43)
	Zygomatic			
	• Arch	2	3	5 (12.20)
	• Body	4	2	6 (14.63)
	Nasal bone	4		4 (9.76)
	Maxillary wall			
	• Anterior			
	• Lateral	1	4	5 (12.20)
		2	5	7 (17.07)
Lower third	Mandible			
	• Condyle	2	1	3 (7.32)
	• Ramus	1		1 (2.43)
	• Body	1		1 (2.43)
	• Symphisis	1		1 (2.43)
	Total			41 (100)

4.4 Glasgow Coma Scale distribution

GCS amongst the subjects were as in Figure 4.3 whereby majority of the subjects (n=12) had full GCS (E4V5M6).The other 3 of them sustained GCS score of 14 (E3V5M6) and 1 subject had score of 13 (E3V4M6). In addition, there were presence of loss of consciousness (LOC) in 4 subjects (25%) and post trauma amnesia (PTA) in 3 subjects (18.8%).

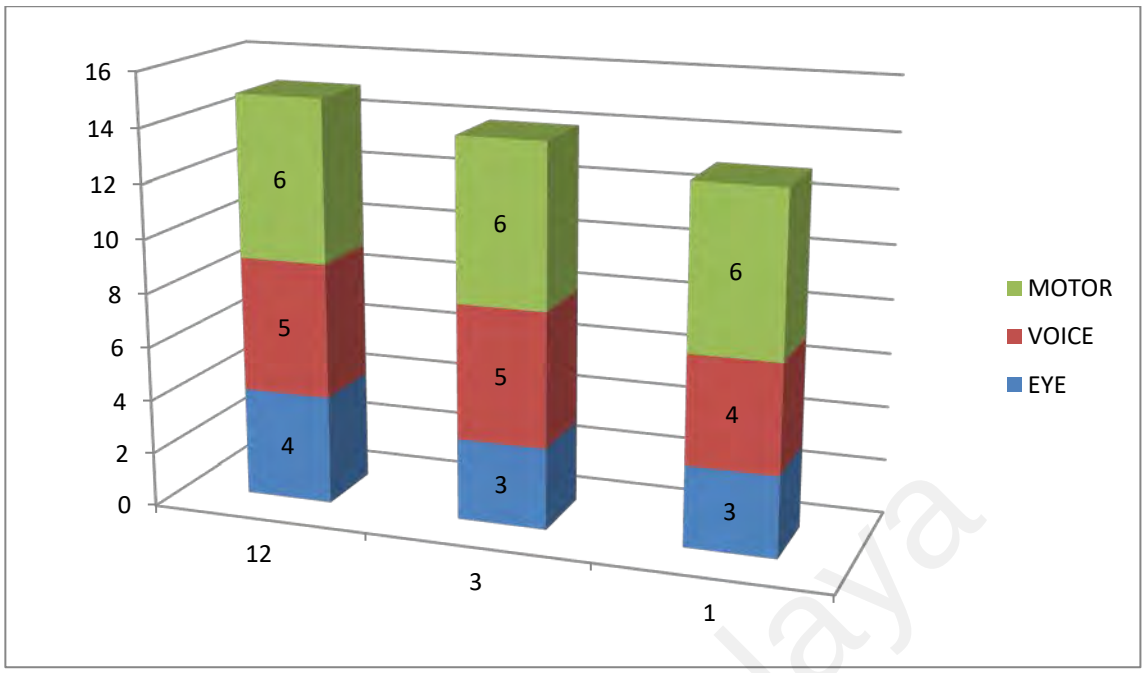

Figure 4.3: GCS distribution amongst subjects

4.5 Difference in HAM-D score and maxillofacial injuries

In Table 4.4, the Kruskal-Wallis test showed that there was no significant difference in HAM-D score in relation to different locations of soft tissue injury for either initial or post 6-month assessment ($p>0.05$). During the initial assessment ($p = 0.585$), the lower third face soft tissue injury had the highest HAM-D score (mean rank = 10.00) followed by injury at mixed location (mean rank = 8.67) and then the upper third injury (mean rank = 6.50). The least HAM-D score was in subjects with middle third injury (mean rank = 5.63). During the 6-month follow-up, it can be noted there were changes in HAM-D score in relation to soft tissue injury location ($p = 0.273$) in which middle third injury scored the highest HAM-D (mean rank = 5.50), followed by upper third (mean rank = 4.00), mixed location injury (mean rank = 3.83) and lower third face (mean rank = 2.00).

Table 4.4: HAM-D score between different locations of soft tissue injury

	Location	Mean rank	p-value
HAM-D initial (n =16)	Upper 1/3 face	6.50	0.585
	Middle 1/3 face	5.63	
	Lower 1/3 face	10.00	
	Mixed	8.67	
HAM-D post 6-month (n = 6)	Upper 1/3 face	4.00	0.273
	Middle 1/3 face	5.50	
	Lower 1/3 face	2.00	
	Mixed	3.83	

In relation to different types of bone fracture, there was no significant difference ($p>0.05$) of HAM-D score during initial and follow up appointment (Table 4.5). The highest score of initial HAM-D ($p = 0.684$) seen in subject with fracture at the upper third portion (mean rank = 10.50). Bone fracture at the lower third area and mixed location had both resulted in lesser HAM-D score (mean rank = 6.50) and the least was in middle third facial bone fracture (mean rank = 6.21). During post 6-month assessment ($p = 0.207$), the middle third facial fracture had the second highest HAM-D score (mean rank = 3.00), then mixed location of fracture (mean rank = 2.00) and lower third facial fracture (mean rank = 1.00). Notably high HAM-D score can also be observed in subjects without facial bone fracture at both initial (mean rank = 9.50) and follow up (mean rank = 5.00) respectively.

Table 4.5: HAM-D score between different types bone fracture

	Location	Mean rank	p-value
HAM-D initial (n = 16)	Upper 1/3 face	10.50	0.684
	Mid 1/3 face	6.21	
	Lower 1/3 face	6.50	
	Mixed	6.50	
	No fracture *	9.50	
HAMD post 6-month (n = 6)	Mid 1/3 face	3.00	0.207
	Lower 1/3 face	1.00	
	Mixed	2.00	
	No fracture *	5.00	

* Soft tissue injury only

4.6 Difference in NSI domain score and maxillofacial injuries

The Kruskal-Wallis result showed that there is no significant relation of NSI domain score to the locations of soft tissue injury at either initial or post 6-month value ($p>0.05$). Table 4.6 showed that during initial assessment, the upper third facial soft tissue injury had attained high NSI score in somatic domain (mean rank = 10.00), as well as cognitive domain (mean rank = 9.00). The NSI score for vestibular domain was increased in mulitple location of soft tissue injury (mean rank = 8.50), while the high sensory and affective domains scores were dominated by injury at the lower third area with mean rank of 9.17 and 8.75 respectively. While in post 6-month assessment, the middle third injury had the highest vestibular, cognitive and affective domains score (mean rank = 6.00) which presented noticeable difference compared to the initial assessment.

Table 4.6: NSI domain score between different locations of soft tissue injury

Location	NSI domain	Initial Mean rank	Initial p-value	Post Mean rank	Post p-value
Upper 1/3 face	Vestibular	7.50	0.859		0.189
Mid 1/3/face		5.63		6.00	
Lower 1/3 face		8.25		2.50	
Mixed		8.50		3.33	
Upper 1/3 face	Somatic	10.00	0.757		0.785
Mid 1/3/face		5.50		2.50	
Lower 1/3 face		8.25		3.75	
Mixed		7.75		3.67	
Upper 1/3 face	Sensory	2.50	0.284		0.216
Mid 1/3/face		5.00		1.50	
Lower 1/3 face		10.00		2.75	
Mixed		9.17		4.67	
Upper 1/3 face	Cognitive	9.00	0.805		0.164
Mid 1/3/face		7.63		6.00	
Lower 1/3 face		6.25		4.00	
Mixed		8.25		2.33	
Upper 1/3 face	Affective	8.50	0.961		0.174
Mid 1/3/face		6.75		6.00	
Lower 1/3 face		8.75		2.00	
Mixed		7.75		3.67	
Upper 1/3 face	Orphan	10.00	0.585		0.368
Mid 1/3/face		6.00		3.00	
Lower 1/3 face		10.25		4.50	
Mixed		7.75		3.00	

In Table 4.7, there is no significant relation of variety NSI domain score to the types of bone fracture, both during either initial or post 6-month evaluation ($p>0.05$). In the vestibular domain, upper third fracture had the highest score (mean rank = 11.00) initially and during post review the score was equal amongst mixed, middle and lower third fracture (mean rank = 2.50). During initial examination, the upper third fracture had also the highest NSI score for cognitive (mean rank = 13.50) and orphan (mean rank = 12.00) domains while both domains were affected mostly in middle third fracture during post 6-month evaluation. Meanwhile for somatic, affective and sensory domains – they were highly susceptible in mixed type fracture (mean rank = 10.00 and 11.00) during initial review, while at follow up the somatic and sensory domains were

increased in middle third fracture (mean rank = 5.00 and 4.00) but for the affective domain, it was highest in mixed location of fracture.

Table 4.7: NSI domain score between different types of bone fracture

Location	NSI domain	Initial Mean rank	Initial p-value	Post Mean rank	Post p-value
Upper 1/3 face	Vestibular	11.00	0.173		0.494
Mid 1/3/face		6.43		2.50	
Lower 1/3 face		3.00		2.50	
Mixed		3.00		2.50	
Upper 1/3 face	Somatic	3.00	0.675		0.630
Mid 1/3/face		7.93		5.00	
Lower 1/3 face		10.00		2.50	
Mixed		10.00		2.50	
Upper 1/3 face	Sensory	7.50	0.670		0.307
Mid 1/3/face		6.07		4.00	
Lower 1/3 face		7.50		1.50	
Mixed		11.00		6.00	
Upper 1/3 face	Cognitive	13.50	0.214		0.657
Mid 1/3/face		6.64		4.00	
Lower 1/3 face		3.50		4.00	
Mixed		3.50		1.50	
Upper 1/3 face	Affective	4.00	0.712		0.531
Mid 1/3/face		6.93		2.00	
Lower 1/3 face		5.50		2.00	
Mixed		10.00		4.00	
Upper 1/3 face	Orphan	12.00	0.597		0.172
Mid 1/3/face		6.00		6.00	
Lower 1/3 face		8.50		3.00	
Mixed		8.50		3.00	

4.7 White matter integrity alteration

Data was analysed using non parametric test, which is Mann-Whitney U to determine the significant different within initial and follow-up assessment between test and control. The significant value was set at α=0.05 with 80% power of the study.

4.7.1 White matter integrity alteration - fractional anisotropy (FA) value

Table 4.8 presents mean rank FA values of test subjects compared to healthy control participants during the acute phase. At baseline, the test group showed significantly lower FA value ($p < 0.001$) when compared to the control group in the middle cerebral peduncle, both inferior cerebellar peduncle, left tapetum, left superior fronto-occipital fasciculus, left uncinate fasciculus and left posterior corona radiata. There were also significantly increased FA values ($p < 0.05$) as seen in bilateral medial lemniscus, right superior cerebellar peduncle, right corticospinal tract, right uncinate fasciculus, right superior longitudinal fasciculus, left retrolenticular of internal capsule and left anterior corona radiata. The remaining tracts showed significantly reduced FA values in test group compared to control.

As depicted in Table 4.9, the mean rank FA values of test subjects compared to healthy control during follow-up showed significant reduced FA value ($p < 0.05$) at middle cerebellar peduncle, pontine crossing tract, inferior cerebellar peduncle and left tapetum. There were also significantly increased FA values ($p < 0.05$) amongst the test group at the left inferior cerebellar peduncle, right superior cerebellar peduncle, left sagittal stratum and left uncinate fasciculus compared to control group. In Table 4.10, there were no significant differences of FA value across time points amongst the test group (n =4).

Table 4.8: Mann-Whitney U test results with significant mean rank of FA between test and control group during initial assessment

No	Variable	Test (n=16) Mean rank	Control (n=16) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	8.5	24.5	<0.001
2	Pontine crossing tract (a part of MCP)	11.0	22.0	0.001
3	Medial lemniscus right	20.0	13.0	0.033
4	Medial lemniscus left	22.2	10.8	0.001
5	Inferior cerebellar peduncle right	8.5	24.5	<0.001
6	Inferior cerebellar peduncle left	8.5	24.5	<0.001
7	Superior cerebellar peduncle right	21.5	11.5	0.003
8	Corticospinal tract right	21.9	11.1	0.001
9	Corticospinal tract left	21.0	12.0	0.007
	Commissure fibre tract			
10	Genu of corpus callosum	13.2	19.8	0.048
11	Body of corpus callosum	11.5	21.5	0.003
12	Tapetum left	8.5	24.5	<0.001
13	Fornix (column and body of fornix)	12.6	20.4	0.018
	Association fibre tract			
14	Fornix (crus) / Stria terminalis right	10.8	22.3	0.009
15	Fornix (crus) / Stria terminalis left	11.6	21.4	0.001
16	Cingulum (cingulate gyrus) right	12.7	20.3	0.023
17	Cingulum (hippocampus) left	12.2	20.8	0.006
18	Superior longitudinal fasciculus right	16.8	16.2	0.003
19	Superior fronto-occipital fasciculus right	12.7	20.3	0.020
20	Superior fronto-occipital fasciculus left	9.8	23.2	<0.001
21	Uncinate fasciculus right	24.3	8.8	0.070
22	Uncinate fasciculus left	16..8	16.3	<0.001
	Projection fibre tract			
23	Retrolenticular part of internal capsule right	12.1	20.9	0.008
24	Retrolenticular part of internal capsule left	21.8	11.2	0.001
25	Anterior corona radiata left	18.4	14.6	0.001
26	Superior corona radiata right	10.9	22.1	0.008
27	Superior corona radiata left	12.1	20.9	0.003
28	Posterior corona radiata left	9.9	23.1	<0.001

Table 4.9: Mann-Whitney U test results with significant mean rank of FA between test and control group during follow-up assessment

No	Variable	Test (n=4) Mean rank	Control (n=4) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	2.5	6.5	0.021
2	Pontine crossing tract (a part of MCP)	2.8	6.3	0.043
3	Inferior cerebellar peduncle right	2.5	6.5	0.021
4	Inferior cerebellar peduncle left	6.5	2.5	0.021
5	Superior cerebellar peduncle right	6.5	2.5	0.021
	Commissure fibre tract			
6	Tapetum left	2.5	6.5	0.021
	Projection fibre tract			
7	Sagittal stratum left	6.3	2.8	0.043
	Association fibre tract			
8	Uncinate fasciculus left	6.5	2.5	0.021

Table 4.10: Wilcoxon Signed Rank test results with mean rank of FA in test group between initial and follow-up assessment

No	Variable	Initial (n=4) Mean rank	Post 6-month (n=4) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	2.5	2.5	0.357
2	Pontine crossing tract (a part of MCP)	0.0	2.5	0.068
3	Inferior cerebellar peduncle right	3.0	2.0	0.715
4	Inferior cerebellar peduncle left	0.0	2.5	0.715
5	Superior cerebellar peduncle right	1.0	3.0	0.068
	Comissure fibre tract			
6	Tapetum left	2.5	2.5	>0.999
	Projection fibre tract			
7	Sagittal stratum left	0.0	2.0	0.109
	Association fibre tract			
8	Uncinate fasciculus left	4.0	2.0	0.715

4.7.2 White matter integrity alteration – mean diffusivity (MD) value

Table 4.11 shows the mean rank MD values of test subjects compared to healthy control participants during the acute phase. At baseline, the test group showed significantly lower MD value ($p < 0.001$) at right superior cerebellar peduncle when compared to the control group. The remaining tracts showed significantly reduced MD values ($p< 0.05$) in test group compared to control in the left fornix crus (stria terminalis), left uncinate fasciculus and left external capsule.

There were also significantly increased MD values ($p < 0.05$) as seen in pontine crossing tract , left corticospinal tract, left tapatum, left cingulum (cingulated gyrus), right cingulum (hippocampus), right superior longitudinal fasciculus, bilateral superior fronto-occipital fasciculus, right uncinate fasciculus and right superior corona radiata.

As depicted in Table 4.12, the mean rank MD values of test subjects compared to control participants during follow-up showed significant reduced FA value ($p < 0.05$) at right superior cerebellar peduncle, left uncinate fasciculus and left external capsule. The FA value in the left corticospinal tract was significantly increased FA values ($p = 0.043$). In Table 4.13, there were no significant differences of FA value across time points amongst the test group ($n =4$).

Table 4.11: Mann-Whitney U test results with significant mean rank of MD between test and control group during initial assessment

No	Variable	Test (n=16) Mean rank	Control (n=16) Mean rank	p-value
	Brainstem tract			
1	Pontine crossing tract (a part of MCP)	20.9	12.1	0.007
2	Superior cerebellar peduncle right	10.1	22.9	<0.001
3	Corticospinal tract left	20.7	12.3	0.012
	Commissure fibre tract			
4	Tapatum left	24.0	9.0	<0.001
	Association fibre tract			
5	Fornix (cres) / Stria terminalis left	12.2	20.8	0.010
6	Cingulum (cingulate gyrus) left	18.8	14.2	0.008
7	Cingulum (hippocampus) right	20.9	12.1	<0.001
8	Superior longitudinal fasciculus right	21.5	11.5	0.003
9	Superior fronto-occipital fasciculus right	22.1	10.9	0.001
10	Superior fronto-occipital fasciculus left	20.1	12.9	0.030
11	Uncinate fasciculus right	19.9	13.1	0.042
12	Uncinate fasciculus left	11.5	21.5	0.003
13	External capsule left	11.7	21.3	0.004
	Projection fibre tract			
14	Superior corona radiata right	20.8	12.2	0.009

Table 4.12: Mann-Whitney U test results with significant mean rank of MD between test and control group during follow-up assessment

No	Variable	Test (n=4) Mean rank	Control (n=4) Mean rank	p-value
	Brainstem tract			
1	Corticospinal tract left	6.3	2.8	0.043
2	Superior cerebellar peduncle right	2.5	6.5	0.021
	Association fibre tract			
3	Uncinate fasciculus left	2.8	6.3	0.043
4	External capsule left	2.5	6.5	0.021

Table 4.13: Wilcoxon Signed Rank test results with mean rank of MD in test group between initial and follow-up assessment

No	Variable	Initial (n=4) Mean rank	Post 6-month (n=4) Mean rank	p-value
	Brainstem tract			
1	Corticospinal tract left	2.5	2.5	>0.999
	Superior cerebellar peduncle right	3.0	2.0	0.715
	Association fibre tract			
2	Uncinate fasciculus left	3.0	1.0	0.144
3	External capsule left	3.0	1.0	0.144

4.7.3 White matter integrity alteration – axial diffusivity (AD) value

The differences of mean rank AD values between test subjects compared to the control group during the initial assessment were pictured in Table 4.14. The test group showed significantly lower AD value ($p < 0.001$) when compared to the control group. at middle cerebellar peduncle, both inferior cerebellar peduncles, right superior cerebellar peduncle, left fornix (crus) stria terminalis and left anterior corona radiata. The remaining tracts AD values ($p< 0.001$) specifically for bilateral corticospinal tracts, right hippocampal cingulum and left retrolenticular part of internal capsule in test group were signifinantly higher compared to control group

While for the follow-up assessment as shown in Table 4.15, there were lesser involved regions of interest with significant AD difference of test subjects compared to control participants. Middle cerebellar peduncle, left inferior cerebellar peduncle, right superior cerebellar peduncle and left fornix (crus) stria terminalis had significantly reduced ($p<0.05$) AD values in test group. In contrary, right medial lemniscus and bilateral corticospinal tract AD values were significantly increased ($p<0.05$) in test group.

Table 4.14: Mann-Whitney U test results with significant mean rank of AD between test and control group during initial assessment

No	Variable	Test (n=16) Mean rank	Control (n=16) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	9.0	24.0	<0.001
2	Medial lemniscus right	20.4	12.6	0.019
3	Medial lemniscus left	20.3	12.8	0.024
4	Inferior cerebellar peduncle right	8.7	24.1	<0.001
5	Inferior cerebellar peduncle left	9.4	23.6	<0.001
6	Superior cerebellar peduncle right	10.3	22.7	<0.001
7	Corticospinal tract right	23.6	9.4	<0.001
8	Corticospinal tract left	23.6	9.4	<0.001
	Commissure fibre tract			
9	Genu of corpus callosum	11.3	21.7	0.002
10	Body of corpus callosum	12.5	20.5	0.015
	Association fibre tract			
11	Fornix (crus) / Stria terminalis right	12.2	20.8	0.009
12	Fornix (crus) / Stria terminalis left	10.0	23.0	<0.001
13	Cingulum (cingulate gyrus) left	20.8	12.3	0.010
14	Cingulum (hippocampus) right	20.4	12.6	0.019
15	Superior fronto-occipital fasciculus left	13.1	19.9	0.040
16	Uncinate fasciculus right	21.2	11.8	0.005
17	Cingulum (cingulate gyrus) right	20.7	12.3	0.011
18	Cingulum (cingulate gyrus) left			0.266
19	Cingulum (hippocampus) right	22.5	10.5	<0.001
20	Cingulum (hippocampus) left	21.2	11.8	0.005
21	External capsule left	12.3	20.8	0.010
	Projection fibre tract			
22	Retrolenticular part of internal capsule right	13.2	19.8	0.044
23	Retrolenticular part of internal capsule left	23.0	10.0	<0.001
24	Anterior limb of internal capsule right	20.6	12.4	0.014
25	Anterior limb of internal capsule left	11.5	21.5	0.003
26	Posterior limb of internal capsule right	20.5	12.5	0.016
27	Anterior corona radiata left	10.7	22.3	<0.001
28	Superior corona radiata left	12.2	20.8	0.010
29	Posterior corona radiata left	11.3	21.7	0.002
30	Posterior thalamic radiation (includeoptic radiation) left	19.9	13.1	0.038
31	Sagittal stratum left	20.4	12.6	0.019

Table 4.15: Mann Whitney U test results with significant mean rank of AD between test and control group during follow-up assessment

No	Variable	Test (n=4) Mean rank	Control (n=4) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	2.5	2.5	0.021
2	Medial lemniscus right	20.4	12.6	0.019
3	Inferior cerebellar peduncle left	2.5	6.5	0.021
4	Superior cerebellar peduncle right	2.5	6.5	0.021
5	Corticospinal tract right	6.5	2.5	0.021
6	Corticospinal tract left	6.5	2.5	0.021
	Association fibre tract			
7	Fornix (cres) / Stria terminalis left	2.8	6.3	0.043

In consistency with the previously discussed DTI parameter amongst test group across time points, there were also no significant differences in AD value (n =4) at all regions (Table 4.16)

Table 4.16: Wilcoxon Signed Rank test results with mean rank of AD in test group between initial and follow-up assessment

No	Variable	Initial (n=4) Mean rank	Post 6-month(n=4) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	3.0	1.0	0.144
2	Medial lemniscus right	3.0	2.0	0.715
3	Inferior cerebellar peduncle left	2.5	2.5	>0.999
4	Superior cerebellar peduncle right	3.0	2.3	0.465
5	Corticospinal tract right	2.5	2.5	>0.999
6	Corticospinal tract left	1.5	3.5	0.465
	Association fibre tract			
7	Fornix (cres) / Stria terminalis left	2.0	2.3	0.715

4.7.4 White matter integrity alteration – radial diffusivity (RD) value

Table 4.17 showed the differences of mean rank RD values were generally higher in test subjects compared to the control group during the initial assessment. This was in contrast to the previously discussed DTI parameter which showed generalised reduction. The test group showed significant increment of RD value ($p < 0.001$) when compared to the control group at middle cerebellar peduncle, both inferior cerebellar peduncles, left tapetum, and left superior fronto-occipital fasciculus .Right superior cerebellar peduncle and left uncinate fasciculus showed significant reduction of RD values ($p<0.001$) in the test group.

During the follow-up assessment as shown in Table 4.18, the higher RD values in test group were significant ($p <0.05$) as during the initial DTI which included middle cerebellar peduncle, both inferior cerebellar peduncles, left tapetum and pontine croosing tract. The trend can be observed also in right superior cerebellar peduncle and left uncinate fasciculus whereby the RD value in test group were reduced significantly ($p<0.021$) which was similar during initial DTI.

However, the intra-group comparison in test participant did not reflect any significant alteration of RD value across two-point times as seen in Table 4.19

Table 4.17: Mann-Whitney U test results with significant mean rank of RD between test and control group during initial assessment

No	Variable	Test (n=16) Mean rank	Control (n=16) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	24.0	9.0	<0.001
2	Pontine crossing tract (a part of MCP)	21.9	11.1	0.001
3	Medial lemniscus left	12.6	20.4	0.018
4	Inferior cerebellar peduncle right	23.4	9.6	<0.001
5	Inferior cerebellar peduncle left	23.1	9.9	<0.001
6	Superior cerebellar peduncle right	10.5	22.5	<0.001
7	Corticospinal tract right	13.6	19.8	0.046
	Commissure fibre tract			
8	Tapatum left	24.5	8.5	<0.001
	Association fibre tract			
9	Superior longitudinal fasciculus right	21.8	11.2	0.001
10	Superior fronto-occipital fasciculus right	22.0	11.0	0.001
11	Superior fronto-occipital fasciculus left	23.3	9.8	<0.001
12	Inferior fronto-occipital fasciculus right	20.2	12.8	0.026
13	Superior longitudinal fasciculus right	21.8	11.2	0.001
14	Uncinate fasciculus left	9.4	23.6	<0.001
15	Cingulum (cingulate gyrus) right	20.7	12.3	0.011
16	Cingulum (hippocampus) right	22.5	10.5	<0.001
17	Cingulum (hippocampus) left	21.2	11.8	0.005
18	External capsule left	12.3	20.8	0.010
	Projection fibre tract			
19	Retrolenticular part of internal capsule right	20.0	13.0	0.033
20	Superior corona radiata right	21.5	11.5	0.002
21	Superior corona radiata left	20.8	12.3	0.010
22	Posterior corona radiate left	18.4	14.6	0.024

Table 4.18: Mann-Whitney U test results with significant mean rank of RD between test and control group during follow-up assessment

No	Variable	Test (n=4) Mean rank	Control (n=4) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	6.5	2.5	0.021
2	Pontine crossing tract (a part of MCP)	6.3	2.8	0.043
3	Inferior cerebellar peduncle right	6.5	2.5	0.020
4	Inferior cerebellar peduncle left	6.3	2.8	0.043
5	Superior cerebellar peduncle right	2.5	6.5	0.021
	Commissure fibre tract			
6	Tapatum left	6.5	2.5	0.021
	Association fibre tract			
7	Uncinate fasciculus left	2.5	6.5	0.021

Table 4.19: Wilcoxon Signed Rank test results with mean rank of RD between test group during initial and follow-up assessment

No	Variable	Initial (n=4) Mean rank	Post 6-month(n=4) Mean rank	p-value
	Brainstem tract			
1	Middle Cerebellar Peduncle	2.5	0.0	0.068
2	Pontine crossing tract (a part of MCP)	2.5	0.0	0.068
3	Inferior cerebellar peduncle right	1.5	3.5	0.465
4	Inferior cerebellar peduncle left	3.0	2.0	0.715
5	Superior cerebellar peduncle right	2.7	2.0	0.269
	Commissure fibre tract			
6	Tapatum left	2.5	2.5	>0.999
	Association fibre tract			
7	Uncinate fasciculus left	2.7	2.0	0.273

4.8 Associations between diffusion tensor imaging parameters and neurobehavioural performance

4.8.1 MRI DTI parameters and NSI domains

A complete longitudinal assessment of WM tract changes and neurobehavioural performance were done at initial stage involving 16 subjects and at post 6-month with 4 subjects. In Table 4.20, the initial FA had multiple negative associations to the WM tract in contrast to the initial MD. FA changes in pontine crossing tract were inversely correlated to most NSI domains involving the vestibular ($r = -0.588$; $p < 0.05$) , cognitive ($r = -0.730$, $p < 0.01$) , affective ($r = -0.600$, $p < 0.05$) and orphan ($r = -0.704$, $p<0.01$), followed by middle cerebellar peduncle in the sensory ($r = -0.549$, $p < 0.05$) , cognitive ($r = -0.644$, $p < 0.05$) and orphan ($r = -0.607$, $p < 0.607$). MD changes in pontine crossing tract had resulted in positive correlation to NSI for the cognitive ($r= 0.582$, $p<0.05$), affective ($r = 0.555$, $p < 0.05$) and orphan domains ($r = 0.535$, $p<0.05$). Other dominating changes were seen in the RD value of middle cerebellar peduncle which were positively correlated to the vestibular ($r = 0.547$,$p < 0.05$), cognitive ($r = 0.616$, $p < 0.05$) and orphan domain ($r= 0.677$,$p < 0.01$) and pontine crossing tract to the cognitive ($r= 0.557$, $p<0.05$), affective ($r = 0.562$, $p < 0.05$) and orphan domains ($r = 0.588$, $p<0.05$) during initial assessment. While during post 6-month; lesser correlation can be appreciated but strikingly, the AD value of right middle lemniscus was positively correlated to vestibular ($r = 0/958$, $p<0.05$) , sensory ($r = 0.968$, $p<0.05$) and cognitive ($r = -0.993$, $p < 0.01$) as presented in Table 4.21.

The HAM-D correlation to DTI parameters were only significant during initial stage as seen in Table 4.22; which were the FA of middle cerebellar peduncle, and pontine crossing tract. The latter MD and and RD values were also shown to have positive correlation to HAM-D.

Table 4.20: Spearman's Correlation Coefficient Table of NSI Against Changes in FA, and MD of the Various Brain Tracts Both at Initial and Post 6-month Assessment

DTI	NSI DOMAINS					
	Vestibular	Somatic	Sensory	Cognitive	Affective	Orphan
Fractional Anisotropy (FA)						
Middle cerebellar peduncle			-0.549*	-0.644*		-0.607*
Pontine crossing tract (a part of MCP)		-0.588*		-0.730**	-0.600*	-0.704**
Inferior cerebellar peduncle right				-0.561*		
Corticospinal tract right				-0.598*		
Corticospinal tract left		-0.588*				
Fornix (crus)/ Stria terminalis right				-0.533*		
Retrolenticular part of internal capsule right				-0.608*		
Inferior cerebellar peduncle left						
Post 6-month						*-0.991***
Mean Diffusivity (MD)						
Pontine crossing tract (a part of MCP)				0.582*	0.555*	0.535*
Corticospinal tract left				0.640*		
Cingulum (hippocampus) right		0.723**				
Superior fronto-occipital fasciculus left		0.565*				
External capsule left						
Initial						0.596*
Post 6-month						*-0.958**
Superior corona radiata right		0.596*				

*Correlation is significant at $p < 0.05$ (two-tailed).
**Correlation is significant at $p < 0.01$ (two-tailed).
Underlined is post 6-month data

Table 4.21: Spearman's Correlation Coefficient Table of NSI Against Changes in AD, and RD of the Various Brain Tracts Both at Initial and Post 6-month Assessment

DTI	NSI DOMAINS					
	Vestibular	Somatic	Sensory	Cognitive	Affective	Orphan
Axial Diffusivity (AD)						
Cingulum (hippocampus) right						
	0.723**					
Retrolenticular part of internal capsule right						
		-0.550*				
Retrolenticular part of internal casule left						
		-0.534*				
Superior corona radiate left						
						0.583*
Posterior corona radiate left						
						0.649*
Middle lemniscus right						
Post 6-month	*-0.958**		*0.968**	*-0.993***		
Radial Diffusivity (RD)						
Middle cerebellar peduncle						
	0.547*			0.616*		0.677**
Pontine crossing tract (a part of MCP)						
Initial				0.557*	0.562*	0.588*
Post 6-month		*0.956**				
Medial lemniscus left						
				0.661**		
Corticospinal tract right						
				0.581*		
Superior fronto-occipital fasciculus left						
				0.558*		0.665**
Cingulum (hippocampus) left						
				0.599*		
Retrolenticular part of internal capsule right						
	-0.538*					
Superior corona radiate right						
	0.559*				-0.588*	
Superior cerebellar peduncle right						
Post 6-month						*0.965**

*Correlation is significant at $p < 0.05$ (two-tailed).
**Correlation is significant at $p < 0.01$ (two-tailed).
Underlined is post 6-month data

Table 4.22 Spearman's Correlation Coefficient Table of HAM-D against Changes in FA, MD and RD of the Various Brain Tracts Both at Initial and Post 6-month Assessment

DTI	HAM-D	
	Initial	Post 6-month
Fractional anisotropy (FA)		
Middle cerebellar peduncle		-0.694*
Pontine crossing tract (a part of MCP)		-0.776**
Mean diffusivity (MD)		
Pontine crossing tract (a part of MCP)		0.687*
Radial Diffusivity (RD)		
Pontine crossing tract (a part of MCP)		0.710**

*Correlation is significant at $p < 0.05$ (two-tailed).
**Correlation is significant at $p < 0.01$ (two-tailed).

CHAPTER 5: DISCUSSION

The relationship between neurobehavioural changes in patients with maxillofacial trauma has not been studied vastly. Moreover, very limited literatures had shown which structural brain changes can cause certain particular changes. With our limited data, we will discuss thoroughly on the MRI DTI changes in maxillofacial trauma subjects with its neurobehavioural presentation. It is important to detect symptoms of these changes; hence early intervention can be made to prevent mental health deterioration in affected patients.

5.1 Maxillofacial trauma

In this study, it has been shown that male were more predominantly involved in motor vehicle accident. The highest age group was between 18-29 years old and is of Malay ethnicity. This is in line with other studies in Malaysia (Ramli et al., 2014; Nordin et al., 2015). Other international literatures had also corroborated that MVA was higher in male and peaked in subjects of 20-30 years of age (Batstone et al., 2007; Salentijn, Peerdeman, et al., 2014). Also in consistence with previous report (Nordin et al, 2015; Veeramuthu et al, 2016) whereby most of the subjects completed 11-12 years of education until secondary level. The accident involved largely motorcyclist in this study which is also common in Malaysia (Hussaini et al., 2007; Abdul Manan & Várhelyi, 2012; Ramli et al., 2014)

In regards to maxillofacial injury, almost all subjects sustained combination of facial bone fracture and soft tissue injury (n=12, 75%). There was a variety patterns of maxillofacial trauma – the most common type was combination of hard and soft tissue injuries with wide range of percentage reported in multiple studies; 44% (Gassner et al., 2003) and 61% (Batstone et al., 2007). Laceration wound was the most common sustained with 50% from all soft tissue injuries and this was also reported in other

studies (Hussaini et al., 2007). Fracture of midfacial area predominated with 82.9% which corresponds with earlier literature (Gonzalez et al., 2015; Nordin et al, 2015) which also in line with higher number of soft tissue injury at the middle 1/3 of facial region (31%).

The concomitant injuries recorded from this study was lesser than previous studies , mainly because of the methodology of this study was to concentrate on maxillofacial trauma subjects with GCS of 13-15 and without major polytrauma. They were only 3; under Ophthalmology for corneal laceration (n=1), Orthopaedic for lower limb fracture (n=1), and Respiratory Surgery for pneumothorax (n=1). Other studies had also shown that the presence of concomitant injuries were almost similar whereby orthopaedic and surgical trauma were involved (Hohlrieder et al., 2004; van Hout et al., 2013).12 subjects recruited had full GCS, while 3 had GCS of 14/15 and 1 was with GCS of 13/15. Mean time taken for full GCS recovery was 4.62 minutes (± 9.03 minutes).

5.2 Neurobehavioural Changes in Maxillofacial Trauma Patients

5.2.1 HAM-D Score in relation to maxillofacial trauma

The result of the present study demonstrated that there was no significant relationship of HAM-D score with regards to maxillofacial trauma for both soft tissue injury and facial bone fracture. However, surprisingly over the two-point time discrepancies, a trend of poor HAM-D score was maintained in subject with soft tissue injury only compared to facial bone fracture. This is believed due to the presence of facial scar and patient perception of facial disfigurement leading to negative response (S. Islam et al., 2012) as well as chronic pain and dysfunction (Shofiq Islam et al., 2010) from the injury.

In our study, one of the soft tissue injury victims was diagnosed with post traumatic stress disorder (PTSD) about a month post trauma and being actively treated with medication and therapy currently. PTSD prevalence had been reported to range from 1.9% to 33% after 1 year (S. Islam et al., 2012)and in maxillofacial trauma, 20-30% of the victims had symptoms of PTSD (Bisson et al., 1997).It developed following acute stress disorder which can be detected about 1 month after trauma (Levin & Diaz-Arrastia, 2015) The predictor factor includes female gender (Cassidy et al., 2014)and memory of the trauma experience which stated higher prevalence (23%) of PTSD in those with a memory than without (6%) (Cassidy et al., 2014). These were true in this particular female subject whom did not sustain any retrograde amnesia and able to recall and re-experience the event.

As for the facial bone fracture; during the initial assessment, the upper third involvement was the most affected group while the middle third fracture had the highest HAM-D score at follow-up evaluation as compare to other facial region. This should be noted that only one case of upper 1/3 fracture was observed in this study and the subject did not attend the follow-up review. There is no previous study that linked specific facial bone fracture type with depression, but it is worth to note that there is positive correlation between depression and facial traumas. An earlier research reported a significant depression score in facial trauma group evaluated using Hospital Anxiety and Depression Scale (HADS) , $p = 0.006$ among 50 subjects (Shofiq Islam et al., 2010).Other research also studied psychiatric sequelae in 50 maxillofacial fracture victims; with 44% (22 patients at post 48-hour post trauma) had acute symptoms of stress, and 26% (13 patients at post 3-month) had post-traumatic stress symptoms. The aesthetic concerns and functional reason particularly scarring, paresthesia and diplopia were the contributing causes (Fabio Roccia, 2005).

5.2.2 NSI Score in relation to maxillofacial trauma

Pertaining to the NSI performance, there were arrays of outcome from maxillofacial trauma affecting specific domain. From the result, however both the soft tissue and hard tissue injuries failed to illustrate significant effect on the neurobehavioral sequelae.

During the initial assessment, the single subject with upper third facial fracture has expressed the worst symptoms on cognitive, vestibular and orphan domains. In concurrence with that, subject sustaining soft tissue injuries on the region had the poorest cognitive and somatic performance.

The multiple facial bone fracture interestingly had the worst symptoms on sensory and affective domains throughout the study. We hypothesized that the greater the intensity of the trauma, the greater impact on psychological and behavioural effects. This is supported by recent data illustrating that subjects who suffered multiple facial (p=0.0097) and mandible (0.0102) fractures reported alteration in their quality of life; at initial and 30-days after the trauma with highest score in functional disability, physical pain and social capacity adapted from Oral Health Impact Profile (Conforte et al., 2016).These published results were quite similar with our study, for instance ; one of the sensory domains affected was alteration in the smell/taste due to presence of blood clot from the fracture; and in affective domain whereby the subjects projected poor frustration tolerance and depression mainly because of their inability to resume daily job; were shown in their report.

The subsequent evaluation at 6-month post trauma revealed that injury on the middle third suffered the most neurobehavioural issues. The affective and vestibular domains were complicated in soft tissue injury, while the bone fracture had implicated the cognitive, somatic and orphan domains. We postulated there might be connection between these domains and clinical signs presented in middle third fracture; a study

(Forouzanfar et al., 2013) showed presence of diplopia (8.5%) and enophthalmos (4.2%) that might cause somatic symptoms like blurring of vision that might exacerbate headache. Another research has shown that following zygmatico-orbital fracture, 19% developed enophthalmos and 50% of the affected victims reported “sunken eye” within 1-week to 1-month post trauma while the doctor detected the problem at 6-month post trauma. The indifferent doctors’ perception towards patients’ complains (Folkestad et al., 2006) may cause undertreatment and failure to address the complain hence the effects it had indirectly onto neurobehaviourial status.

There is newer evidence from a study that demonstrated subjects with maxillofacial trauma in conjunction with mild traumatic brain injury (mTBI) without any intracranial lesion had increased risk of short and long term neurocognitive derangement in comparison with subjects having all the three diagnoses. The involved maxillofacial injuries were fractures in the upper and middle third facial regions and they had poorer recovery in cognitive domain; exclusively executive function, memory and attention (Veeramuthu et al., 2016).

The lower third facial soft tissue injury had resulted in the least consequence. It caused sensory and affective issues during initial assessment which improved later on follow-up. While the lower third facial bone fracture demonstrated better NSI score in which it contribute the least to NSI symptoms in every domain. In the contrary, an earlier study in regards to mandibular fracture was carried out exclusively amongst impoverished samples. They had revealed that there was significant depression, anxiety, hostility, phobia and obsessive-compulsive in injured subjects compared to the control. Nevertheless, the research did not exclude subject with illegal substance use (47% had the history of abusing street drugs) use as compared to our study (Lento et al., 2004)

Currently, there is a lacking of studies showing the effect of maxillofacial trauma to behavioural changes as against its relation to mild traumatic brain injury (mTBI). Fundamentally, these limited studies of facial trauma collectively proposed the importance of psychological symptoms evaluation in facial trauma patients as an intervention to treat the disorder via pharmacological mean, education and psychological support (Glynn et al., 2003; Hull et al., 2003). Some studies also suggested for multidisciplinary team to tackle psychological issues in facial injury patients (Fabio Roccia, 2005; Ukpong et al., 2007). This is vital as early treatment hopes to dampen the development of chronic PTSD or maladaptation, such as alcohol or drugs abuse

5.3 DTI MRI in Maxillofacial Trauma Patients

During the acute period, there were significant differences between test and control pertained to FA, MD, AD and RD values in almost half of the 50 ROI tracts. However, the longitudinal investigation revealed drastic reduction of number of significant involved tracts. Most importantly, there was no significant difference between the test group at acute and chronic evaluation.

Table 5.1: Comparison of MRI DTI variables of test to control group during initial assessment

White matter tract	FA	MD	AD	RD
	(mean rank ; test vs control)			
Brainstem tract				
Middle Cerebellar Peduncle	↓		↓	↑
Pontine crossing tract (a part of MCP)	↓	↑		↑
Medial lemniscus right	↑		↑	
Medial lemniscus left	↑		↑	↓
Inferior cerebellar peduncle right	↓		↓	↑
Inferior cerebellar peduncle left	↓		↓	↑
Superior cerebellar peduncle right	↑	↓		↓
Corticospinal tract right	↑		↑	
Corticospinal tract left	↓	↑	↑	
Commissure fibre tract				
Genu of corpus callosum	↓		↓	
Body of corpus callosum	↓		↓	
Tapetum left	↓	↑		↑
Fornix (column and body of fornix)	↓			
Association fibre tract				
Fornix (crus) / Stria terminalis right	↓		↓	
Fornix (crus) / Stria terminalis left	↓	↓	↓	
Cingulum (cingulate gyrus) right	↓		↑	↑
Cingulum (hippocampus) left	↓	↑	↑	↑
Superior longitudinal fasciculus right	↑	↑	↑	↑
Superior fronto-occipital fasciculus right	↓	↑		↑

Superior fronto-occipital fasciculus left	↓	↑	↓	↑
Uncinate fasciculus right	↑	↑	↑	
Uncinate fasciculus left	↑	↓	↓	↓
External capsule left		↓	↓	↓
Projection fibre tract				
Retrolenticular part of internal capsule right	↓	↓	↑	
Retrolenticular part of internal capsule left	↑		↓	
Anterior corona radiata left	↑		↓	
Superior corona radiata right	↓	↑		
Superior corona radiata left	↓		↓	↑
Posterior corona radiata left	↓		↓	↑
Anterior limbic of internal capsule right			↑	
Anterior limbic of internal capsule left			↓	
Posterior limbic of internal capsule right			↑	
Poesterior thalamic radiation left			↓	
Sagittal stratum			↑	

As shown in Table 5.1, there were various significant differences in all DTI parameters. In DTI MRI, water molecule movement is measured within a volume element (voxel). As discussed earlier, the water movement in the white matter is restricted due to presence of axonal membrane, thus anisotropic. Generally, following this rule it is comprehended that in area of organized axon orientation, the FA will be higher because of the water molecule restriction e.g. internal capsule or corpus callosum

(FitzGerald & Crosson, 2011).Contradictorily, FA is reduced in less organised white matter after mTBI due to loss of neuronal integration thus resulted in lesser restriction of water movement . However, the FA can also be increased in specific voxel with crossing fibres if the loss of axons is greater along one axis causing more restriction to water movement (Assaf & Pasternak, 2008).

Other parameters include mean diffusivity (MD); represents average water diffusion value across all directions of movement, axial diffusivity (AD); represents longitudinal diffusion of water to white matter tract and radial diffusivity (RD); represents perpendicular diffusion of water to white matter tract. Thus, the higher AD values reflect lower water diffusion hence, better white matter integrity. Opposing these are higher RD values which are the signs of higher water diffusion in reduced white matter integrity. From these basic understanding, the parameters can be used to assist in detecting white matter alteration (Waller et al., 2017).

In addition, a report (Veeramuthu et al., 2015)had shown presence of these findings during acute stage;

i. Low FA, high MD and high RD – indicates vasogenic brain oedema (extracellular oedema). This is due to the release of intracellular protein into brain parenchyma.
ii. High FA, low MD and low RD – indicates cytotoxic oedema (intracellular oedema). It has poorer outcome than the above.
iii. High FA, high MD and unchanged RD – indicates reactive astrogliosis (migration of astrocytes to injured site), hence increase cells density and reduce diffusivity of affected area.

FA values has been observed to reduce in corona radiata, anterior limb of internal capsule, superior longitudinal fasciculus, optic radiation and genu of corpus callosum

and were significantly lower in TBI group of MVA origin (Veeramuthu et al., 2015). FA reduction was also observed in genu and splenium of corpus callosum and it show an affiliation with poor visual memory, also in TBI subjects (Holli et al., 2010).

In addition, lower FA values in corpus callosum, cingulum and centrum semi-ovale both during acute and chronic stage of mTBI. Regarding MD value, increment was noted in splenium of corpus callosum, while RD values were increased in genu and splenium of corpus callosum (Miles et al., 2008).

From this study, it can be observed that during acute setting, more specific white matter tracts were affected. These brain architectural defects in maxillofacial trauma subject can be related to the effect of biomechanic and biophysic during the MVA which includes mechanism of trauma, the force conveyed to the facial skeleton and the impact borne by the maxillofacial skeleton (Salentijn, Collin, et al., 2014; Veeramuthu et al., 2016).

5.4 DTI MRI and Neurobehavioral Changes

From the result, it was proven that there were higher numbers of involved WM tract changes causing significant alteration in NSI domains and HAM-D scores acutely as compared to chronic stage. These WM tracts included middle cerebellar peduncle, pontine crossing tract, inferior cerebellar peduncle, corticospinal tract, fornix/stria terminalis, cingulum (hippocampus), retrolenticular part of internal capsule, and superior fronto-occipital fasciculus with cognitive, vestibular and orphan domains were the most frequently affected.

In a published report, similar observations of acute DTI changes in middle cerebellar peduncle and cingulum were significantly associated with cognitive deficits (Veeramuthu et al., 2015). It was believed that neuronal network reorganization, glial

scarring and disturbance of the cortical and subcortical brain structures post-trauma contributed to these changes (Gerrish et al., 2014)

Nonetheless, the possibility of direct neurobehavioural implications on DTI MRI in subjects should not be excluded. There was a particular systematic review discussing on the matter of DTI MRI relationship and depression ; and TBI respectively (Maller et al., 2010). The associated changes in depression included reduced FA at the frontal and temporal brain region, frontal gyrus, corpus callosum, amygdala and hippocampus (Taylor & Krishnan, 2008). The main difference was that the mean age for depression was 54.5 years old to that of 32.3 years in TBI subject suggesting that WM alteration seen was in line with natural occurring event in aging brain.

CHAPTER 6: CONCLUSION

6.1 Conclusion

Maxillofacial trauma in GCS of 13-15 has been shown to have effects on the microstructural architecture of certain brain white matter tracts significantly ($n = 22$, $p < 0.005$) during the acute stage of the event as compared to healthy controls. However, yet these subtle changes had not been of strong impact to the neurobehavioural performance of these sufferers ($p > 0.005$). The post 6-month revealed incredible improvement of these white matter changes whereby reduction of more than 50% of the total number of involved tracts.

Nonetheless, this study had shown there were more neurobehavioural derangements noted over the times in middle third facial bone fracture from NSI assessment. This could be related to the factor that middle third fracture had the highest rate amongst other injuries (82.9%). Astonishingly, maxillofacial soft tissue injury alone contributed to the highest HAM-D score even the presence was low ($n = 4$, 25%) with one subject was diagnosed with PTSD.

This showed there was a possibility of maxillofacial trauma injury to cause brain changes altogether the behaviour presentation though not significant. This may merit the need not only to produce periodically systematic follow-up in terms of the physical clinical presentation of maxillofacial injury itself, but to incorporate the emotional and mental status during clinical assessment. The maxillofacial surgeons should equip themselves with the knowledge of behaviour alteration signs in order to be able to assist the patients throughout the recovery process. Moreover, the reality of maxillofacial injury occurred not only within controlled environment as in this research. Other co-factors such as medical conditions and habits pre-trauma that may change the behaviour status post-trauma should be addressed as well.

6.2 Limitations

Overall, there were many challenges faced during the process of carrying out the projects. There were essentially small numbers of subjects during the initial assessment furthermore during the latter. The difficulty in accumulating sample was particularly due to strict inclusion criteria as more of the maxillofacial trauma patients may not be due to MVA only, nor were not all Malaysian and free of pre-morbidity.

Other was due to low second revisit rate; despite earlier reminder prior to the appointment. The limited slots for MRI DTI which were held on Thursday and Tuesday each week were irrelevant as the timeframe of 24-48 hours post injury should be adhered strictly. This has caused under usage if suitable candidate is not available within the allocated time.

6.3 Recommendations

In conclusion, there are few recommendations that might be executed to improve the outcome of this study.

i. To study the different effect of maxillofacial treatment to the neurobehavioural outcome in terms of surgical and non-surgical intervention.
ii. To investigate white matter changes in maxillofacial trauma subjects of different aetiology other than MVA, thus enables the surgeon to predict the outcome.
iii. To collect data from multiple centres in order to have better study population.

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APPENDICES

APPENDIX A: ASSESSMENT PRO FORMA

PRO FORMA : ORAL AND MAXILLOFACIAL INJURY Pg 1/2

Patient Particulars : Registration Sticker

Telephone / Contact Details:

Date of admission:
Time of trauma:
Admission delay:

Time of admission:
Nationality & Race: / 1 Malay 2 Chinese 3 Indian 4
Mechanism of trauma:
1 Pedestrian
2 Motorcycle vs Motorcycle
3 Motorcycle vs Car
4 Car vs Car
5 Cyclist
6 Others:

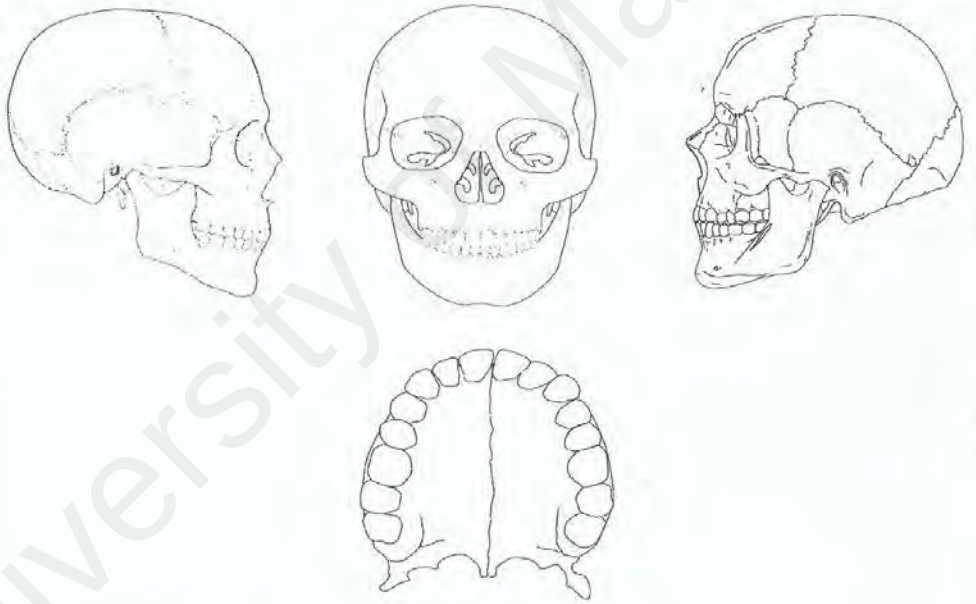
Best GCS on Arrival:

Eyes	Motor	Verbal	
/4	/6	/5	/15

Pupils on admission: Rt Lt

Type of Injury:
Mild (13-15)
Moderate (9-12)
Severe (=<8)

Please illustrate the details of fracture in the following diagram:



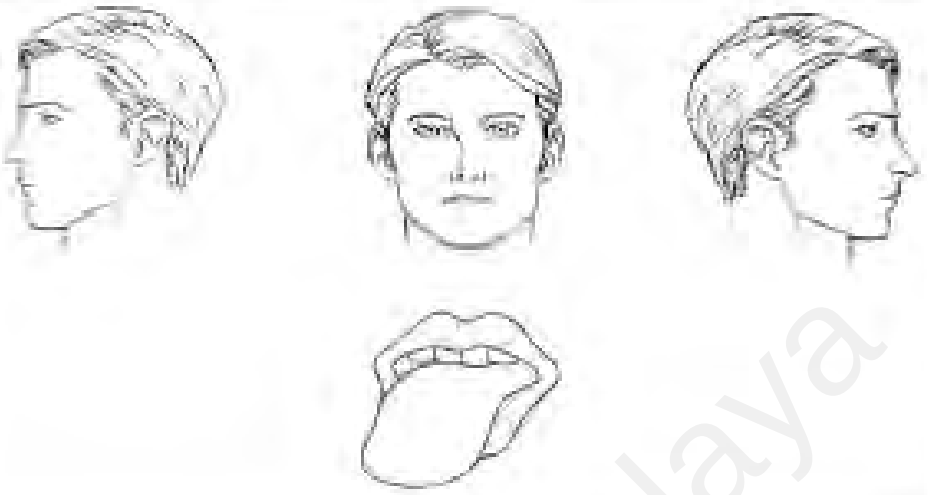
Notation: Types of fracture - Comminuted (C) , Hairline (H) , Depressed (D) , Linear (L) , Split (S)

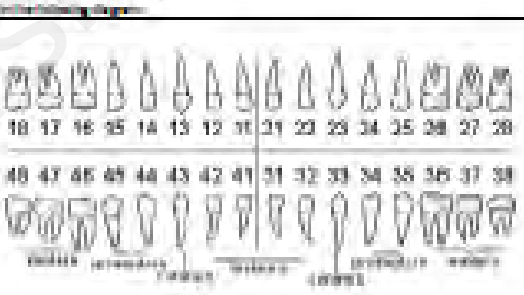
Detailed examination of fracture based on clinical and radiological examination:

Frontal bone :

Midface portion :

Mandible :





APPENDIX B: NSI TOOL

Page 1

Date:
Name:
Medical Record #:

Neurobehavioral Symptom Inventory (NSI)

Please rate the following symptoms with regard to how much they have disturbed you IN THE LAST 2 Weeks.
The purpose of this inventory is to track symptoms over time. Please do not attempt to score.
0 = None – Rarely if ever present; not a problem at all
1 = Mild – Occasionally present, but it does not disrupt my activities; I can usually continue what I'm doing; doesn't really concern me.
2 = Moderate – Often present, occasionally disrupts my activities; I can usually continue what I'm doing with some effort; I feel somewhat concerned.
3 = Severe – Frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel I need help.
4 = Very Severe – Almost always present and I have been unable to perform at work, school or home due to this problem; I probably cannot function without help.

Symptoms	0 1 2 3 4
1. Feeling Dizzy	O O O O O
2. Loss of balance	O O O O O
3. Poor coordination, clumsy	O O O O O
4. Headaches	O O O O O
5. Nausea	O O O O O
6. Vision problems, blurring, trouble seeing	O O O O O
7. Sensitivity to light	O O O O O
8. Hearing difficulty	O O O O O
9. Sensitivity to noise	O O O O O
10. Numbness or tingling on parts of my body	O O O O O
11. Change in taste and/or smell	O O O O O
12. Loss of appetite or increased appetite	O O O O O
13. Poor concentration, can't pay attention, easily distracted	O O O O O
14. Forgetfulness, can't remember things	O O O O O
15. Difficulty making decisions	O O O O O
16. Slowed thinking, difficulty getting organized, can't finish things	O O O O O
17. Fatigue, loss of energy, getting tired easily	O O O O O
18. Difficulty falling or staying asleep	O O O O O
19. Feeling anxious or tense	O O O O O
20. Feeling depressed or sad	O O O O O
21. Irritability, easily annoyed	O O O O O
22. Poor frustration tolerance, feeling easily overwhelmed by things	O O O O O

APPENDIX C: HAM-D TOOL

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name

Date of Assessment

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

_____
- **0=** Absent
- **1=** These feeling states indicated only on questioning
- **2=** These feeling states spontaneously reported verbally
- **3=** Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
- **4=** Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

_____
- **0=** Absent
- **1=** Self reproach, feels he has let people down
- **2=** Ideas of guilt or rumination over past errors or sinful deeds
- **3=** Present illness is a punishment. Delusions of guilt
- **4=** Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

_____
- **0=** Absent
- **1=** Feels life is not worth living
- **2=** Wishes he were dead or any thoughts of possible death to self
- **3=** Suicidal ideas or gesture
- **4=** Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**

_____
- **0=** No difficulty falling asleep
- **1=** Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
- **2=** Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**

_____
- **0=** No difficulty
- **1=** Patient complains of being restless and disturbed during the night
- **2=** Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

Adapted from Hedlung and Vieweg, The Hamilton rating scale for depression, *Journal of Operational Psychiatry*, 1979;10(2):149-165.

6. **INSOMNIA LATE**

_____
0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**

_____
0= No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness

8. **RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____
0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. **AGITATION**

_____
0= None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. **ANXIETY (PSYCHOLOGICAL)**

_____
0= No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. **ANXIETY SOMATIC:** Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity. "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____
- **0=** None
- **1=** Loss of appetite but eating without encouragement from others. Food intake about normal
- **2=** Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____
- **0=** None
- **1=** Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
- **2=** Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____
- **0=** Absent
- **1=** Mild
- **2=** Severe

15. HYPOCHONDRIASIS

_____
- **0=** Not present
- **1=** Self-absorption (bodily)
- **2=** Preoccupation with health
- **3=** Frequent complaints, requests for help, etc.
- **4=** Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:
- **0=** No weight loss
- **1=** Probably weight loss associated with present illness
- **2=** Definite (according to patient) weight loss
- **3=** Not assessed

17. INSIGHT

_____
- **0=** Acknowledges being depressed and ill
- **1=** Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- **2=** Denies being ill at all

18. DIURNAL VARIATION

_____ **A.** Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
- **0=** No variation
- **1=** Worse in A.M.
- **2=** Worse in P.M.

_____ **B.** When present, mark the severity of the variation. Mark "None" if NO variation
- **0=** None
- **1=** Mild
- **2=** Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

_____
0= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____
0= Absent
1= Mild
2= Severe

Total Score _____

Presented as a service by

GlaxoWellcome

 Printed in USA. WEL0569D February 1997

APPENDIX D: FACULTY OF DENTISTRY

ETHICS APPROVAL

UNIVERSITY OF MALAYA

MEDICAL ETHICS COMMITTEE
FACULTY OF DENTISTRY
ADDRESS: 50603, KUALA LUMPUR, MALAYSIA
TELEPHONE: 03-79676461 FAXIMILE: 03-79676456

NAME OF ETHICS COMMITTEE/IRB: Medical Ethics Committee, Faculty of Dentistry ADDRESS: Faculty of Dentistry, University of Malaya, 50603, Kuala Lumpur	ETHICS COMMITTEE/IRB REFERENCE NUMBER:
PROTOCOL NO: TITLE: Pure Maxillofacial Trauma and its Correlation with Neurobehavioural Alteration amongst Malaysian: A Longitudinal Study	DF OS1621/0067(P)
PRINCIPAL INVESTIGATOR: Dr. Firdaus bin Hariri / Dr. Nor 'Izzati Mohtar TELEPHONE: 012-3375120	

The following item [√] have been received and reviewed in connection with the above study to be conducted by the above investigator.

[√] Investigator's Checklist — Ver date: 14 June 2016
[√] Application Form — Ver date: 1 Sept 2016
[√] Approval Form for Presentation at Department
[√] Brief CV of Main Investigator
Patient Information Sheet (PIS):
[√] BM version
[√] English version
[ ] Others: _____
Consent Form:
[√] BM version
[√] English version
[ ] Others: _____
[√] Questionnaire
[√] Approval letter from Head of Biomedical Imaging UMMC

and have been

[√] Approved
[ ] Conditionally approved (identify item and specify modification below or in accompanying letter)
[ ] Rejected (identify item and specify reasons below or in accompanying letter)

Investigator are required to:
1) follow instructions, guidelines and requirements of the Medical Ethics Committee.
2) report any protocol deviations/violations to Medical Ethics Committee.
3) comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki
4) note that Medical Ethics Committee may audit the approved study.
5) Please update your project status (on-going/ completed) by submitting study report/ study closure report form (UM-DMEC-SR01).

Approval period: 1 Sept 2016 – 31 July 2017

c.c Dean
Faculty of Dentistry

Head
Department of Oral and Maxillofacial Clinical Sciences

Secretary
Medical Ethics Committee
Faculty of Dentistry

PROF. DR. NOOR HAYATY ABU KASIM
Chairperson
Medical Ethics Committee

APPENDIX E: RESEARCH GRANT

UNIVERSITI MALAYA

UM.D/DRMC/628/6/1
01 Ogos 2016

Dr. Nur Izzati binti Mohtar (DGJ 140006)
Jabatan Sains Klinikal Mulut & Maksilofasial
Fakulti Pergigian, UM

Puan,

PERMOHONAN PERUNTUKAN PENYELIDIKAN PASCASISWAZAH SECARA 'COURSEWORK': PPPC/C1-2016/DGJ/01

Dengan hormatnya merujuk kepada perkara di atas.

2. Sukacita dimaklumkan bahawa permohonan geran puan telah diluluskan oleh Ahli Jawatankuasa Penyelidikan Fakulti dan butiran adalah seperti berikut:

Tajuk Penyelidikan : Pure maxillofacial trauma and its correlation with neorobehavioural alteration amongst Malaysian: Alongitudinal study
Penyelia Projek : Dr. Firdaus Bin Hariri

VOT	JUMLAH KELULUSAN (RM)
Vot 21000 (Travel)	NA
Vot 27000 (Research Materials)	6,161.40
Vot 28000 (Maintenance and Laboratory Fees)	NA
Vot 29000 (Special Services)	1,200.00
Vot 35000 (Equipment) >3,000/ <3,000	NA
JUMLAH KELULUSAN	**7,361.40**

3. Sebarang penggunaan peruntukan adalah tertakluk kepada bajet asal (rujuk lampiran) yang telah dikemukakan dan dipersetujui oleh AJK pada tarikh surat ini dikeluarkan. Sebarang perubahan penggunaan peruntukan daripada permohonan asal, puan perlu menulis surat rasmi kepada pihak kami.

4. Satu sesi taklimat berkaitan penggunaan peruntukan tersebut melalui sistem E-Research Management akan diadakan seperti berikut:

Tarikh : 05 Ogos 2016 (Jumaat)
Masa : 3.00 petang
Tempat : Bilik Komputer, Aras 6, Bangunan Pascaijazah & Penyelidikan, Fakulti Pergigian, UM

Katanama dan katalaluan akan dimaklumkan kepada pemohon pada sesi taklimat tersebut. Surat asal ini perlu disimpan sebagai rujukan.

Sekian, terima kasih.

Yang benar,

PROF. MADYA DR. ZAMRI RADZI
Timbalan Dekan (Penyelidikan & Pembangunan)

s.k. - Dekan, Fakulti Pergigian
- Ketua Jabatan Sains Klinikal Mulut & Maksilofasial
- Dr. Firdaus Bin Hariri, Penyelia projek
- Pegawai Kewangan, Fakulti Pergigian, UM
- Pn. Norshida Manan, Pembantu tadbir DRMC

ZR/ishlpc1-16

Pusat Pengurusan Penyelidikan Pergigian (DRMC), Tingkat 6, Bangunan Pascaijazah & Penyelidikan, Fakulti Pergigian, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
Dental Research Management Centre (DRMC), 6th Floor, Postgraduate & Research Tower, Faculty of Dentistry, University of Malaya, 50603 Kuala Lumpur, Malaysia
Tel: (603) 7967 6451 / 7967 6455 • Fax: (603) 7967 6456 • E-mail:rmc_dental@um.edu.my • Website: http//dentistry.um.edu.my

APPENDIX F: PATIENT/PARTICIPANT INFORMATION SHEET

PATIENT/PARTICIPANT INFORMATION SHEET

Please read the following information carefully. Do not hesitate to discuss any questions you may have with your doctor.

Study Title: PURE MAXILLOFACIAL TRAUMA AND ITS CORRELATION WITH NEUROBEHAVIOURAL ALTERATION AMONGST MALAYSIAN : A LONGITUDINAL STUDY

Introduction:

Accidents usually cause a lot of injuries in our body. It can be in the form of soft tissue e.g. contusions/ laceration wounds; or facial bone fractures. The impact from the force could actually transmit to the brain which has many vital nerves structures.

What is the purpose of this study?

1. The purpose of this study is to investigate whether the injuries sustained through accidents could actually cause micro injuries to the brain.
2. If there are injuries noted in the brain, will it alter daily chores and routine activity of the person?

What are the procedures to be followed?

If you agree to participate in this study, you are required :

1. To undergo imaging called Diffusion Tensor Imaging (DTI), this will take about 30 minutes to complete the entire scanning procedure.

2. To answer the questionnaire and this will take about 30 – 40 minutes to complete the entire assessment.

3. ***To come for follow up after 6 months and should be able to undergo DTI and participate in answering the questionnaire again.***

The DTI imaging procedure is free of charge and will be reimbursed by the research grant.

Who should not enter the study?

1. If you have any systemic diseases such as diabetes mellitus or hypertension.
2. If you are under alcohol or drug influence

What will be the benefits of the study:

(a) To your child/you as a subject?

If micro brain injuries were identified, you will be referred for further neuropsychological assessment.

(b) To the investigator?

To identify whether injury to the face cause brain injuries.

What are the possible drawbacks?

Drawback will be if you are claustrophobic – DTI may become a concern

Can I refuse to take part in the study?

Your participation is totally voluntary. You need not have to explain why you prefer not to take part in the study and it will not affect your dental treatment.

Who shall I contact if I have additional questions during the course of the study?

Main and other investigators (all listed in the application form):

(1) Investigator's Name: DR. NOR 'IZZATI MOHTAR
Mobile No.: 012 - 7606345
Address: Department of Oro-Maxillofacial Surgical & Medical Sciences, UM
Email address: izzati.mohtar@ummc.edu.my

(2) Investigator's Name: DR. FIRDAUS BIN HARIRI
Mobile No.: 012-3375120
Address: Department of Oro-Maxillofacial Surgical & Medical Sciences, UM
Email address: firdaushariri@um.edu.my

(3) Investigator's Name: PROF DR VAIRAVAN NARAYANAN
Mobile No.: 012- 6058432
Address: Department of Surgery,Medical Faculty, UM
Email address: nvairavan@hotmail.com

(4) Investigator's Name : DR VIGNESWARAN VEERAMUTHU
Mobile No.: 010-2258602
Address: Department of Surgery, Medical Faculty, UM
Email address : vicveera@gmail.com

APPENDIX G: PATIENT/PARTICIPANT INFORMATION SHEET

(MALAY TRANSLATION)

BORANG MAKLUMAT KEPADA PESAKIT/PESERTA

SILA BACA MAKLUMAT BERIKUT DENGAN TELITI, DAN SEKIRANYA ADA APA-APA SOALAN, SILA BINCANGKAN DENGAN DOKTOR BERKENAAN.

Tajuk kajian: PURE MAXILLOFACIAL TRAUMA AND ITS CORRELATION WITH NEUROBEHAVIOURAL ALTERATION *AMONGST MALAYSIAN* : A LONGITUDINAL STUDY

Pengenalan:

Kemalangan jalan raya biasanya akan menyebabkan kecederaan pada tisu lembut seperti bengkak atau luka, dan keretakan tulang muka. Impak ke arah muka dari mekanisme kemalangan boleh menyebabkan kecederaan yang tidak diingini di bahagian otak.

Apakah tujuan kajian ini?

1. Untuk mengetahui sama ada kecederaan yang dialami dari kemalangan turut membabitkan kecederaan mikro di bahagian otak.
2. Untuk mengetahui bahawa sekiranya ada kecederaan mikro di bahagian otak, adakah kecederaan ini akan mengganggu aktiviti harian.

.

Apakah langkah-langkah perlu diikuti?

1. Perlu melalui proses pengimejan – Diffusion Tensor Imaging (DTI) yang akan mengambil masa selama 30 minit.

2. Perlu menjawab beberapa soalan yang akan dikemukakan, biasanya sesi ini akan mengambil masa selama 30 – 40 minit.

3. ***Perlu datang semula selepas 6 bulan dan sudi melalui proses pengimejan dan sesi soal jawab semula.***

Prosedur DTI ini adalah percuma dan ditanggung oleh geran kajian.

Siapakah tidak layak diterima untuk kajian?

Sekiranya anda mempunyai masalah kesihatan seperti kencing manis atau darah tinggi.

Atau sekiranya anda di bawah pengaruh alkohol atau dadah.

Apakah manfaat kajian ini:

(a) Kepada anak/anda anda sebagai pesakit?

Sekiranya kecederaan mikro di bahagian otak dikenalpasti, rujukan untuk rawatan selanjutnya akan dilakukan.

(b) Kepada penyelidik?

Untuk mengetahui sama ada kecederaan ringan di bahagian kepala boleh menyebabkan kecederaan di bahagian otak.

Apakah halangan kajian ini?

Sesiapa yang mempunyai ketakutan/ fobia di tempat atau ruang yang sempit – ketika proses DTI.

Bolehkan saya menolak dari menyertai kajian ini?

Penyertaan anda adalah secara sukarela. Anda tidak perlu untuk menjelaskan sebab anda tidak memilih untuk mengambil bahagian dalam kajian ini dan ia tidak akan menjejaskan rawatan pergigian anda.

Siapakah patut saya berhubung sekiranya ada soalan tambahan sepanjang masa kajian ini?

Penyiasat utama dan penyiasat-penyiasat lain (seperti yang tersenarai dalam Borang Permohonan):

(1) Nama penyelidik: : DR. NOR 'IZZATI MOHTAR
No. Telefon Bimbit: 012 - 7606345
Alamat: Department of Oro-Maxillofacial Surgical & Medical Sciences, UM
Alamat Email: izzati.mohtar@ummc.edu.my

(2) Nama penyelidik: DR. FIRDAUS BIN HARIRI
No. Telefon Bimbit: 03 - 79674807
Alamat: Department of Oro-Maxillofacial Surgical & Medical Sciences, UM
Alamat Email: firdaushariri@um.edu.my

(3) Nama penyelidik: PROF DR VAIRAVAN NARAYANAN
No. Telefon Bimbit.: 012- 6058432
Alamat: Department of Surgery,Medical Faculty, UM
Alamat Email: nvairavan@hotmail.com

(4) Nama penyelidik : DR VIGNESWARAN VEERAMUTHU
No. Telefon Bimbit: 010-2258602
Alamat: Department of Surgery, Medical Faculty, UM
Alamat Email : vicveera@gmail.com

APPENDIX H : CONSENT FORM

I, ……Identity Card No…….....
(Name of patient)
of…….....
(Address)

hereby agree to take part in the clinical research (clinical study) specified below :

Title of Study : PURE MAXILLOFACIAL TRAUMA AND ITS CORRELATION WITH NEUROBEHAVIOURAL ALTERATION AMONGST MALAYSIAN: A LONGITUDINAL STUDY the nature and purpose of which has been explained to me by Dr…… *(Name & designation of doctor)* and interpreted by……*(Name & designation of interpreter)*to the best of his/her ability in……. language/dialect.

I have been told about the nature of the clinical research in terms of methodology, possible adverse effects and complications (as per the patient information sheet). After knowing and understanding all the possible advantages and disadvantages of this clinical research, I voluntarily consent of my own free will to participate in the clinical research specified above.

I understand that I can withdraw from this clinical research at any time without assigning my reason whatsoever and in such a situation shall not be denied the benefits of usual treatment by the attending doctors.

Date …… Signature or thumbprint…….....
(Patient)

IN THE PRESENCE OF

Name …….....
I/C No. …… Signature …….....
(Witness for signature of patient)
Position ……..... Date .....

I confirm that I have explained to the patient the nature and purpose of the above mentioned clinical research.

Date ……..... Signature …….....
(Attending doctor)

CONSENT BY PATIENT FOR CLINICAL RESEARCH

R.N.
Name
Age
Unit

APPENDIX I: CONSENT FORM (MALAY TRANSLATION)

Saya, ……...No. Kad Pengenalan... .....
(Nama pesakit)
beralamat…….....
(Alamat)
dengan ini bersetuju menyertai dalam penyelidikan klinikal (pengajian klinikal/pengajian soalselidik/percubaan ubat-ubatan) disebut berikut:

Tajuk Penyelidikan ***: Kajian Berterusan tentang Perkaitan antara Kecederaan Trauma pada Muka dan Rahang berserta Perubahan Psikologi Tingkah-laku di Kalangan Rakyat Malaysia)*** yang mana sifat dan tujuannya telah diterangkan kepada saya oleh Dr…….....*(Nama &jawatandoktor)* mengikut terjemahan ……... *(Nama & jawatan penterjemah)* yang telah menterjemahkan kepada saya dengan sepenuh kemampuan dan kebolehannya di dalam bahasa/loghat…… .

Saya telah diberitahu bahawa dasar penyelidikan klinikal dalam keadaan metodologi, risiko dan komplikasi (mengikut kertas maklumat pesakit). Selepas mengetahui dan memahami semua kemungkinan kebaikan dan keburukan penyelidikan klinikal ini, saya merelakan/mengizinkan sendiri menyertai penyelidikan klinikal tersebut di atas.

Saya faham bahawa saya boleh menarik diri daripada penyelidikan klinikal ini pada bila-bila masa tanpa memberi sebarang alasan dalam situasi ini dan tidak akan dikecualikan dari doktor yang merawat.

Tarikh …… Tandatangan/Cap jari…….....
(Pesakit)

DI HADAPAN

Nama …….....
No. K/P ……..... Tandatangan ……
(Saksi untuk tandatangan pesakit)
Jawatan …… Tarikh..... .....

Saya sahkan bahawa saya telah menerangkan kepada pesakit tentang sifat dan tujuan penyelidikan klinikal tersebut di atas.

Tarikh …….. Tandatangan …….....
(Doktor yang merawat)

KEIZINAN OLEH PESAKIT
UNTUK
PENYELIDIKAN KLINIKAL

No. Pend.
Nama
Jantina
Umur
Unit