EFFECTS OF COMBINATIONS OF PRE-OPERATIVE SUBMUCOSAL METHYLPREDNISOLONE WITH DIFFERENT POST-OPERATIVE ANALGESIC AGENTS IN PAIN CONTROL FOLLOWING SURGICAL REMOVAL OF IMPACTED THIRD MOLAR

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RESEARCH REPORT SUBMITTED TO THE DEPARTMENT OF ORAL AND MAXILLOFACIAL CLINICAL SCIENCES, FACULTY OF DENTISTRY, UNIVERSITY OF MALAYA, IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER'S IN CLINICAL DENSTISTRY (ORAL AND MAXILLOFACIAL SURGERY)

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Field of Study : **Oral and Maxillofacial Surgery**

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ABSTRACT

Introduction : Mandibular third molar is the most frequently impacted tooth and surgical removal of impacted mandibular third molar is the most common performed surgical intervention in dentistry. As any other surgeries, the procedure possesses risks of complications. The common sequelae of mandibular third molar surgery are post-operative pain, facial swelling and trismus. These occur as a result of natural inflammatory process which often affect patients' ability to perform their daily activities thus, compromise their quality of life. Attempts to reduce the post-operative complications after third molar surgery have been made using variety of anti-inflammatory drugs and the usage corticosteroids has been extensively studied. **Objective :** The objective of this study is to evaluate the effects of combinations pre-operative submucosal methylprednisolone with different post-operative analgesics in pain control following surgical removal of impacted third molars. **Methods :** This study is a prospective randomised clinical trial performed on 60 subjects by one single operator. Patients were divided randomly into 3 groups. Group 1 received pre-operative submucosal methylprednisolone with post-operative ibuprofen, Group 2 received pre-operative submucosal with post-operative paracetamol whereas Group 3 was the control group received only post-operative ibuprofen. Baseline measurement and subsequent assessments were made on post-operative day 1, 2 and 7. Data was analysed with SPSS version 24.0 with p-value set at <0.05 as significant. **Result :** Post-operative evaluation showed that there was a significant difference between the study and control group on VAS score in post-operative 4, 6, 7 and 8 hours (p-values <0.05). There was no significant difference between the two methylprednisolone groups in VAS score (p-value >0.05). Both methylprednisolone groups showed lower VAS score at post-operative day 2 and 7 although they were not statistically significant (p-value >0.05) as compared to the control group. It was observed that patients in control group also consumed more rescue

analgesics as compared to methylprednisolone groups. **Conclusion :** Patients given pre-operative submucosal injection of 40mg methylprednisolone before surgical removal of impacted third molar did show significant pain control post-operatively. This beneficial effect was seen mostly at day one post-operative.

ABSTRAK

Pendahuluan : Gigi geraham bongsu pada rahang bawah merupakan gigi yang paling selalu terimpak dan pembuangan gigi tersebut secara pembedahan merupakan prosedur

paling kerap dilakukan di dalam praktis pergigian. Seperti mana-mana pembedahan, pembuangan gigi geraham bongsu ini juga mempunyai risiko-risiko komplikasi. Komplikasi paling kerap disebabkan oleh prosedur ini termasuklah kesakitan selepas pembedahan, bengkak pada bahagian muka dan bukaan mulut terhad. Ini terjadi disebabkan oleh proses keradangan yang berlaku secara semula jadi kesan daripada pembedahan yang mengakibatkan pesakit-pesakit tidak dapat menjalakan aktiviti harian seperti biasa seterusnya memberi kesan kepada kualiti hidup. Pelbagai usaha untuk mengurangkan kesan keradangan selepas pembedahan telah dilakukan menggunakan ubat-ubatan anti-keradangan tetapi penggunaan ubat *corticosteroids* sebagai agen anti-keradangan adalah yang paling banyak dikaji. **Objektif :** Kajian ini dijalankan bertujuan untuk mengkaji kesan gabungan submukosal *methylprednisolone* sebelum pembedahan dengan ubat tahan kesakitan yang berbeza selepas pembedahan bagi kawalan kesakitan selepas cabutan gigi bongsu secara pembedahan. **Methode :** Kajian ini merupakan kajian prospektif, percubaan klinikal secara rawak melibatkan 60 subjek kajian yang dilakukan oleh seorang operator. Pesakit-pesakit dipecahkan kepada tiga kumpulan secara rawak. Kumpulan 1 menerima *submucosal methylprednisolone* sebelum pembedahan dengan ubat Ibuprofen selepas pembedahan. Kumpulan 2 menerima *submucosal methylprednisolone* sebelum pembedahan dengan ubat Paracetamol selepas pembedahan. Manakala, kumpulan 3 merupakan kumpulan kawalan hanya menerima ubat Ibuprofen selepas pembedahan. Ukuran awal sebelum pembedahan dan penilaian kesan pembedahan dijalankan pada hari pertama, kedua dan ke-tujuh selepas pembedahan. Data yang diperolehi dianalisa dengan menggunakan SPSS versi 24.0 dan *p-value* ditetapkan pada <0.05 untuk dianggap sebagai perbezaan ketara. **Keputusan :** Keputusan daripada kajian ini mendapati bahawa terdapat perbezaa ketara pada skor kesakitan VAS pesakit selepas pembedahan antara kumpulan yang menerima methylprednisolone dan kumpulan kawalan untk jam 4, 6,7 dan 8 (*p-value* <0.05). Tiada perbezaan ketara dilihat antara

kedua-dua kumpulan yang menerima *submucosal methylprednisolone*. Skor kesakitan VAS untuk kumpulan yang menerima *methylprednisolone* dilihat lebih rendah berbanding kumpulan kawalan walaupun tiada perbezaan ketara secara statistic selepas pembedahan pada hari kedue dan ke-tujuh. Kajian juga mendapati kumpulan kawalan menggunakan ubat tahan sakit penyelamat lebih banyak berbanding kumpulan yang menerima *Methylprednisolone*. **Penutup :** Pesakit-pesakit yang diberi submucosal 40mg methylprednisolone sebelum pembedahan menunjukkan kawalan kesakitan yang lebih ketara berbanding kumpulan kawalan. Kesan baik ubat ini boleh dilihat selepas pembedahan walaupun pada hari pertama.

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LIST OF SYMBOLS AND ABBREVIATIONS

AA	:	Arachidonic acid
AMPA	:	α-Amino-3-hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ANOVA	:	Analysis of variance
ASA	:	American Society of Anaesthesiology
ATP	:	Adenosine triphosphate
CGRP	:	Calcitonin gene-related-peptide
CN	:	Cranial Nerve
COX	:	Cyclooxygenase
DAC	:	Diacylglycerol
EP	:	Endoperoxide
GABA	:	Gamma-Aminobutyric acid
GR	:	Glucocorticoids receptor
GRS	:	Graphic rating scale
HMW	:	High molecular weight
IASP	:	International Association for the Study of Pain
IL-1	:	Interleukin-1
IL-6	:	Interleukin-6
IP_3	:	Inositol 1,4,5-triphoshphate
LOX	:	Lipooxygenase
MAPK	:	Mitogen Activated Protein Kinase
mGluR	:	Metabotropic Glutamate Receptor
MP	:	Methylprednisolone
NK	:	Neurokinin
NMDA	:	N-Methyl-D-Aspartate

NRS	:	Numerical rating scale
NSAID	:	Non-steroidal anti-inflammatory drug
PCM	:	Paracetamol
PGE2	:	Prostaglandin E2
PGs	:	Prostaglandins
PKC	:	Protein Kinase C
PLA2	:	Phospholipase A2
POD	:	Post-operative day
P2X	:	Purinoreceptor
RSC	:	Receptor-steroid complex
SADRRS	:	Spontaneous Adverse Drug Reaction Reporting System
SD	:	Standard deviation
SPSS	:	Statistical Package for Social Sciences
STAT	:	Signal Transducer and Activator of Transcription
TNF-α	:	Tumour Necrosis Factor-α
TNFR	:	Tumour Necrosis Factor Receptor
TP	:	Thromboxane/Prostaglandin
VAS	:	Visual analogue scale
WHO	:	World Health Organization

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 Introduction

Impacted wisdom tooth is one of the most common pathology of oral cavity. It occurs as a tooth failed to completely erupt and attain its normal functional position due to lack of space in the dental arch. A tooth can be either partially or completely unerupted, positioned against another tooth or can be either soft tissue or bony impaction. Mandibular third molar is the most frequently impacted tooth. Most often when patient with impacted third molar seek treatment; the impacted tooth is probably indicated for extraction either due to caries or recurrent pericoronitis aimed to relieve pain or referred for facilitation of orthodontic treatment as well as prevention of future complications such as formation of dentigyrous cyst (Lee et al., 2015). Surgical removal of impacted third molar is one of the common surgical procedure performed in dentistry. Complication rate following surgical removal of impacted third molar may vary between 2.6% to 30.9% (Deliverska & Petkova, 2016) and its severity depends on many factors such as, the difficulty of the extraction, the extent of surgical trauma, operator's expertise, tobacco smoking and patient's oral hygiene (Rakhshan, 2015). Third molar surgery complications can either be inflammatory (eg: facial swelling, trismus and post-operative pain) or iatrogenic (eg: nerves injury or bone fractures). Although complication rate is relatively low, they can severely affect patient's quality of life especially during immediate post-operative period. A surgical incision produces tissue injury, inflammation and consequently pain. Therefore, acute post-operative surgical pain is actually a normal physiological response to the damage induced to tissues. Inflammation has long been considered as a defence mechanism, with two main events involved which are vascular reaction and cellular event, aims to neutralise and remove injurious stimuli and inflammatory mediators as well as to promote tissue repair (Mitchell & Contran, 2003).

In the event of inflammation, inflammatory mediators are secreted at the site of injury to stimulate further nociceptor activation. This is known as the' inflammatory soup' and is made up of chemicals such as peptides (eg: bradykinin), neurotransmitters (eg: serotonin), lipids (eg: prostaglandins) and neutrophins (eg: nerve growth factors) (Dinakar & Stillman, 2016). The presence of these molecules excites the nociceptor and lower the pain threshold, thus, increase the intensity of the pain sensation. A variety of anti-inflammatory medications have been used in attempts to reduce surgical pain. One of them is corticosteroid. Corticosteroids inhibit the action of phospholipase and thus prevent the formation of arachidonic acid and subsequently the inflammatory mediators. Knowing that inflammatory mechanism contributes to the post-operative surgical pain, it is expected that administration of corticosteroids pre-operative or intra-operative would ameliorate the post-operative inflammation.

Despite previous studies showing efficacy of different types of corticosteroids and routes of administration, post-operative pain control reported was not to be as good as reduction of post-operative swelling and trismus. Therefore, this study combines the use of different groups of analgesic with pre-operative submucosal injection of 40mg methylprednisolone to investigate combinations that can provide a better post-operative pain control.

The result of this study can be used as a treatment regime, not only in cases of impacted mandibular third molar surgeries but also other dentoalveolar surgeries, for better post-operative pain control. The outcome of this study can be adapted into current treatment protocol to provide a more comfortable post-operative recovery period.

1.2 Aim

To investigate the effects of combinations of pre-operative submucosal methylprednisolone with different post-operative analgesic agents in pain control following third molar surgery

1.3 Objective

i. To investigate the effects of combinations of pre-operative submucosal methylprednisolone with Paracetamol or Ibuprofen in pain control following third molar surgery.
ii. To determine the analgesic effect of submucosal methylprednisolone in third molar surgery.
iii. To investigate the effect of combination of pre-operative submucosal methylprednisolone with Paracetamol or Ibuprofen in reducing swelling and trismus following third molar surgery.

CHAPTER 2: LITERATURE REVIEW

2.1 Inflammation

Inflammatory response related to surgery or trauma is considered as surgical inflammation, resulted largely from local release of mediators that then act systematically, involving series of overlapping successive phases. The proposed theory of acute inflammatory response to mechanical injury is based on the pathological functional predominance of nervous, immune and endocrine systems (Arias, Aller, & Arias, 2009), which represent the consecutive phases of the response to stress developed by the body from the injured tissues.

The first pathological activity of acute inflammation following tissue damage from surgical insult is the stimulation of the nociceptors and activation of the pain pathways. There is upregulation of the ionic channel expression in the nociceptive circuits that causes spontaneous neural firing reflecting the nervous phase of the process. This is followed by the immune phase, characterised by activation of the complement cascade and the release of inflammatory mediators (eg: cytokines, chemokines and prostaglandins) acting as pain mediators and modulators. Several biochemical mediators involved in the pain process particularly histamine, bradykinin, prostaglandins and substance P, lead to sensitisation of free nerve endings and involved in oedema formation. The late endocrine phase plays role in the regenerative and repair process of the damaged tissues involving neo-angiogenesis and formation of scar tissue in the presence of growth factors (Arias et al., 2009).

Clinically, acute inflammation is characterised by 5 cardinal signs; redness *(rubor)*, increased heat *(calor)*, swelling *(tumor)*, pain *(dolor)* and loss of functions *(functio laesa)*. Pain as one of the cardinal features of inflammation has long been of interest for research.

Pain is essentially a perceptual process that arises in response to some activities of mechanical insult. International Association for the Study of Pain (IASP) described pain as unpleasant sensory and emotional experience associated with actual and potential tissue damage (K. H. Kumar & Elavarasi, 2016). The process by which the unpleasant noxious stimulus from the periphery is transmitted through the spinal cord and various area of the central nervous system is called nociception and resulting in the physiological sensation of pain and associated negative emotional response, ultimately results in the sensation of pain (Dinakar & Stillman, 2016).

2.2 Pain and pain pathway

2.2.1 General pain pathway

Pathogenesis of surgical pain starts with conversion of a stimulus in the periphery at the nociceptive sensory fibres into an action potential in a process called as transduction. A nerve impulse is created if the stimulus is of enough intensity to reach the threshold for action potential. The impulse propagates along the primary afferent fibres to reach the central nervous system. The first order afferent neuron is a pseudo-unipolar in which a single process divides into both a peripheral and a central axon and its cell bodies are located in the posterior root or cranial root ganglia.

The primary somatosensory fibres are divided into 3 large groups. The first group comprises of the A-α, A-β or A-γ, which are involved in the touch and proprioception. The other 2 groups, namely A-δ fibres and C fibres, are involved with the noxious perception. A-δ fibres is a myelinated nerve which is responsible for sharp pain sensation. In contrast, the C fibres which is involved in dull aching pain perception is an unmyelinated nerve. Both A-δ and C fibres are polymodal and respond to noxious mechanical, thermal and chemical irritant stimuli.

The sensation of pain is mediated by numerous intra-cellular and extra-cellular molecular messengers. Nociceptors upon activation transmit the information via glutamate signalling which is an excitatory neurotransmitter. The presence of inflammatory chemicals modulates the transduction and transmission process by causing excitation of the nociceptors and lowering the pain threshold. Some of the involved substances include globulin and protein kinase, released from the damaged tissue can actively produce pain. Prostaglandin, which is metabolised from arachidonic acid released during tissue damage, blocks potassium efflux from nociceptors and makes them more sensitive. Tissue damage also stimulates mast cells to release histamine, which subsequently excites nociceptors and causes pain. Substance P and calcitonin gene-related peptide are also released by the inflammation or tissue damage increasing the intensity of nociceptors activation and transmission of the impulses. Similarly, serotonin, acetylcholine and adenosine triphosphate and release of lactic acid due to increased metabolism also excite nociceptors.

The primary afferent neuron enters the spinal cord or brainstem and synapses with secondary somatosensory neuron. The information from activated nociceptor fibres is relayed to the spinal cord by the sensory cells located in the dorsal root ganglia, in which the lateral division of the dorsal root ganglion fibres contains most of the small myelinated and unmyelinated axons carrying pain and temperature signals. The grey matter at this area is arranged in a pattern of lamination and the classification proposed by Rexed is based on the function of each lamina (Dinakar & Stillman, 2016). Central sensitisation happened when the axons bringing the information from periphery to the Rexed layer release neurochemical agents such as glutamate, vasoactive peptide, somatostatin and substance P which activates the nociceptive neurons in the spinal cord. Pain sensation is being modulated within the layers, mainly the Rexed layer I and II, before it is ultimately being transmitted to the central nervous system via the anterior spinothalamic tract.

The second-order neuron crosses the midline and form the spinothalamic tract which then ascend to the ventral posterolateral nucleus of the thalamus. From the thalamic nuclei, neuron project upward to the somatosensory cortex of the post-central gyrus, insula and some other cortical areas to form the third-order neuron. These are the primary cortical areas receiving information about sharp pain and are organized in a somatotopic map to allow for accurate localisation of pain. In contrast, insula and rostral cingulate gyrus involved in receiving information on dull or deep-pain information. Along their course through the brainstem, spinothalamic fibres give off many collaterals to the reticular formation functions to modulate the sensory perception, motor activity and behavioural responses.

The descending nociceptive pathways is a more complicated system. Pain modulation occurs via opioid receptors and GABA receptors in the peripheral and central nervous system. Inhibition of pain processing and analgesia resulted from stimulation of the receptors by opiates or endogenous opiates such as endorphin, encephalin and dynorphin, which are governed by the descending modulatory pain system. GABA acts by augmenting the descending inhibition of spinal nociceptive neurons. The descending pathway originated from the medulla, brainstem, hypothalamus and the cortex interact with afferent fibres, interneurons and projections from the dorsal horn. Action at these sites either suppress or enhance the passage of nociceptive information to the periaqueductal grey, thalamus, hypothalamus, amygdala and other structures involved in secondary processing to modulate the activity of the descending pathways.

2.2.2 Trigeminal pain pathway

Trigeminal nerve (CN V) is the principal sensory nerve of oro-facial structures. The sensory fibres pass from the periphery to their cell bodies in the trigeminal ganglion located at the floor of middle cranial fossa. From the ganglion the nerve fibres pass centrally to trigeminal nuclei complex, consists of the principal trigeminal nucleus as well as the spinal descending trigeminal nuclei. The trigeminal spinal tract is subdivided from rostral to caudal into sub-nucleus oralis, sub-nucleus inter-polaris and sub-nucleus caudalis. Sub-nucleus caudalis has been implicated in the trigeminal nociceptive mechanism based on the electrophysiological observations of neurons (Capra & Dessem, 1992).

In trigeminal pain pathway, the first-order neurons from free nerve ending of CN V carry impulses directly into the brainstem in the region of pons to synapse with the trigeminal spinal nucleus. Second-order trigeminal neurons project to the thalamus from the synaptic junction with the primary afferents in the sub-nucleus caudalis. Most of second-order neurons in the spinal dorsal horn and trigeminal nucleus cross the midline to the contra-lateral side and ascend to the thalamus via the spinothalamic and trigeminothalamic tracts. Axons of second-order neurons synapse with the third-relay neurons in the thalamus. The third-order neurons then project to different areas in the sensory cerebral cortex and to the limbic system of the forebrain. These impulses contribute to the sensory-discriminative and affective-emotional component of pain.

As the surgical procedure activates the inflammatory process, a variety of inflammatory mediators and signalling molecules released and actively contribute to the inflammatory response and modify the pain processing. They come from the circulatory system, inflammatory cells as well as from the injured tissues.

2.3 Inflammatory mediators and signalling molecules

2.3.1 Pro-inflammatory cytokines

Cytokines are now recognized as one of the important mediators of inflammatory pain. Neurons can be either be activated directly by cytokines binding to the cell surface receptors or be sensitised directly or indirectly leading to increased responsiveness to stimulation. During the acute phase, cytokines appear to induce sensitisation via receptor-associated kinases and phosphorylation of ions channel. The indirect pathway involves stimulation of the inflamed tissues to release agents such as prostaglandins. Cytokines influence the intracellular modulating process of pain, binds to its specific membrane-bound receptor leading to a cascade of phosphorylation and expression of signal proteins within the cell. Examples of intracellular signal proteins involve in nociception or pain are mitogen activated protein kinase (MAPK), Ras/Raf, c-jun, c-fos, and signal transducer and activator of transcription (STAT). Interestingly, these signal proteins are also involved in the intracellular signal pathways of several cytokines, including IL-6 which then modulate the pathogenesis of pain.

IL-6 which is synthesised after nerve injury in the peripheral nerves, dorsal root ganglia and in the spinal cord, has been a focus of interest in the study of pain. Administration of IL-6 in the skin provokes pain, and experimental pain increases if IL-6 is injected in the cerebrospinal fluid (De Jongh et al., 2003). IL-6 is produced in substantial quantities at the site of a surgical wound. The concentration of the cytokine enters the systemic circulation correlates to the severity of the surgery or the magnitude of tissue injury. This leads to intensification of the post-operative pain. On the other hand, IL-1 is a polypeptide synthesised by inflammatory cells, has shown to have role in mediating the inflammatory process by inducing production of prostaglandin E2 (PGE_2). Role PGE_2 is well known in the pathogenesis of pain, the fact that it sensitises nociceptors to a variety of noxious stimuli. Until now, the present experiments conducting on IL-1

support the concept that IL-1 increases pain reflex and this is mediated by PGE_2 (Schweizer et al, 1988). There is increasing evidence that tumour necrosis factor-α (TNF-α), a major pro-inflammatory cytokine, produced by immune system and both peripheral and central nervous system has critical role in pathogenesis of pain. TNF-α has the capability to modulate the activity of multiple ion channels such as Na+, K+, Ca+ and capsaicin receptor which induce spontaneous activity in primary sensory neurons. Its role in central nervous system is mainly enhancing synaptic transmission of pain signals and causing hyperexcitability in the dorsal horn neurons. This is achieved through the effect two structurally related and functionally distinct receptors, TNF receptor 1 (TNFR-1) and TNF receptor-2 (TNFR-2). Recent evidences show the important role of TNF-α in inflammatory pain by regulating the central sensitization especially the neuronal and synaptic plasticity (Leung & Cahill, 2010).

2.3.2 Neurotransmitters

2.3.2.1 Adenosine triphosphate

Adenosine triphosphate (ATP) is an essential metabolite involved in energy transfer. Both adenosine and ATP can influence nociceptive transmission by their functions as extracellular signalling molecules and actions on cell surface receptors. Upon released into the extracellular milieu from the damaged tissue, it directly stimulates the nociceptive neurons. This happens following metabolism of ATP into adenosine by ectonucleotides and binds to its receptors that are located at the peripheral site of the sensory neurons and centrally on the second-order neurons in the dorsal horn ganglia. Receptor for ATP is ionotropic purinoreceptors (P2X), with six different types. However, one receptor, $P2X_3$ is of interest in pain pathways as it is relatively selectively expressed at high level by the nociceptive neurons (Sawynok, 2007). Once ATP binds to its receptors, Na^+ ions can cross the membrane via their channels and induce membrane depolarisation, activating

Ca^2-sensitive intracellular processes and causing both pain and hyperalgesia. ATP can also indirectly act on the nociceptors to increase the release of glutamate. Both will lead to activation of the nociceptors and modulate the pain process.

2.3.2.2 Glutamate

Glutamate, a carboxylated amino acid, derived from glutamine via the action of phosphate-activated glutaminase and biosynthesised in the mitochondrion and stored in vesicles in the axons. Glutamate is the most abundant excitatory neurotransmitter in the nervous system and involved in pain sensation and transmission. It is released by the increased in the intracellular Ca^{2+} activity due to activation of voltage gated Ca^{2+} channels. It is released in the synaptic cleft blind and binds to its receptors on the postsynaptic receptors. Glutamate mediates its effects via two broad types of receptors; ionotropic and metabotropic receptors. There are 3 families of ionotropic receptors; N-Methyl-D-Aspartate (NMDA) group and the non-NMDA group. The latter group of receptors are divided into the Kainate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptors. NMDA is an agonist receptor, in which upon binding, may trigger action potential in the postsynaptic neurons. Both AMPA and Kainate receptors are also agonist receptor, generally mediate spinal monosynaptic reflexes and acute nociceptive responses (Fernandez-Montoya et al, 2017). However, the presence of AMPA is important to regulate the action of NMDA receptors as these receptors have an internal binding site for Mg2+ ions which act as a voltage-dependent block. So, NMDA rely on the excitatory postsynaptic current produced by AMPA to open the blockage. The metabotropic receptors (mGluRs) on the other hand, are a diverse receptor group, the products of eight genes belonging to a larger family of C-class of G-protein coupled receptors. The receptors have been segregated into 3 group based on their amino acid sequence. Group I which consists of mGluR I and V, group II

consists of mGluR II and mGluR III and the last group is group III which consists of mGluR IV, VI, VII and VIII. All metabotropic receptors are agonist in nature, in which upon activation will lead to transmission of nociceptive impulses from presynaptic end to the post-synaptic neurons (Wozniak, Rojas, Wu, & Slusher, 2012).

2.3.3 Neuropeptides

2.3.3.1 Substance P

Neuropeptides are now considered as major determinants of the inflammatory process in peripheral tissues, a phenomenon known as neurogenic inflammation. Substance P is one of the common neuropeptides and more representative involved in neurogenic inflammation. Besides substance P, some other neuropeptides such as calcitonin gene-related-peptide (CGRP) and neurokinin A-B (NK A&B) also have pro-inflammatory property. Substance P is produced in the subset of capsaicin sensitive sensory peripheral neuron cell bodies localised in dorsal root ganglia and trigeminal ganglia. It plays a pivotal role in transmission of noxious stimuli in the spinal cord. The biological effects of released substance P are induced following its binding to the G protein-coupled neurokinin (NK) receptors. There are 3 types of NK receptors; NK 1, NK 2 and NK 3, which are shown to exhibit preferences for substance P, NK A and NK B. It is worth to mention that these receptors are found at high concentrations in dental tissues. Interaction between substance P and its receptor induces vasodilatation with increased blood vessel permeability and allows plasma extravasation and mast cells degranulation. This leads to release of histamines which in turn further amplifies vascular process and activates nociceptors. Inflammatory cells upon stimulated by substance P, produce inflammatory mediators such as prostaglandin E2 (PGE2), thromboxane and proinflammatory cytokines such as IL-1, IL-6 and TNF-α. These molecular events ultimately sustain the synthesis and release of new substance P and therefore perpetrating the vicious cycle.

This mechanism does not involve only nerve fibres at the site of tissue damage but also extended to the surrounding undamaged tissues and causes secondary hyperalgesia. On this basis, substance P is considered as a major mediator for neurogenic inflammation and associated hyperalgesia (Sacerdote & Levrini, 2012).

2.3.4 Inflammatory mediators

2.3.4.1 Bradykinin; Kinin-Kallikrein system

Bradykinin, biologically active kinins, are short-lived peptides mediator generated by the enzymatic action of kallikreins on kininogen precursors. It is one of the most potent pain-producing agents formed under inflammatory condition. Kinins can be synthesised both intravascularly and extra-vascularly in tissues. These peptides are cleaved from their protein precursors, kininogen by proteolytic enzymes. Conversion of high molecular weight (HMW) kininogen to bradykinin is mediated by plasma kallikrein. Pre-kallikrein is transformed into kallikrein in response tissue damage and inflammation. Bradykinin preferentially acts on B_2-receptors. B_2-receptors are found at a constant density on various cells such as smooth muscle, postganglionic sympathetic fibres and nociceptive primary afferent neurons (Petho & Reeh, 2012).

Upon binding to its receptors, bradykinin induces activation of phospholipase C (PLC), an enzyme that is important in the intracellular signalling, subsequently activates inositol 1,4,5-triphoshphate (IP_3) and diacylglycerol (DAC). DAC mediates most of the excitatory effects of bradykinin, by activating the protein kinase C (PKC), PKC causes phosphorylation of ion channels to both Na^+ and K^+. This leads to membrane depolarisation and generation of action potential. PKC also shown to induce elevation of intracellular Ca^{2+} concentration in somatosensory neurons. Increase intracellular Ca^{2+} concentration primarily due to release of intracellular storage and secondarily due to

influx of Ca^{2+}, both cause independent action potential firing. Bradykinin can lead to a release of arachidonic acid in cultured sensory neurons, and this response was shown to depend on influx of extracellular Ca2+. This is achieved via activation of phospholipase A2 (PLA2) through a G protein and can result in arachidonic acid formation in sensory neurons. Arachidonic acid release may lead to production of prostanoids (prostaglandins and thromboxane) and leukotrienes by COX and lipoxygenase (LOX) enzymes, respectively.

2.3.4.2 Prostaglandin

Prostanoids including prostaglandins (major members are PGE2, PGI2, PGD2 and PGF2α) and thromboxane are derivatives from arachidonic acid. These derivatives are from the activity of cyclooxygenase (COX) enzymes. After tissue injury, release of proinflammatory cytokines and other inflammatory mediators such as substance P, bradykinin and histamine results in plasma extravasation and activation of arachidonic acid cascade leading to production of prostaglandins. Arachidonic acid (AA) is a 20-carbon poly-unsaturated fatty acid produce from membrane phospholipids from the activity of phospholipase A2 (PLA2) and it is the precursor for prostaglandin synthesis via the COX pathway. The release of the fatty acid from the phospholipid is the first control point in the PGs biosynthetic pathway. The second control point is the enzyme responsible converting the fatty acid to the first molecule in the relevant pathway. There are two enzymes primarily involved in the eicosanoid biosynthesis namely prostaglandin synthase or cyclooxygenase and lipoxygenase. Cyclooxygenase exists in 2 isoforms, the COX1 and COX2, which catalyse the oxidation of AA to prostanoids. COX1 is being predominantly constitutive enzymes and plays role in the production of prostanoids that control normal physiological process. On the other hand, COX2 is mainly inducible and

is responsible for the production of proinflammatory prostaglandins that cause inflammation and pain.

Prostanoids act on G protein-coupled prostanoid receptors, which consist of several types, subtypes and splice variants. However, the most important prostanoids receptors in inflammation are EP receptors which are preferring the PGE2 and TP receptors which have affinity to TCA2. PGE2, binding to different EP receptors, can regulate the function of many cell types including macrophages, dendritic cells and T and B lymphocytes leading to both pro- and anti-inflammatory effects. PGE2 has shown to enhance T-cell activation and regulate cytokines expression. It also plays role during neuroinflammation. Noxious stimuli induce the synthesis and release of PGE2 causing more damage to the tissues, activate the nociceptors and enhance pain transmission. It changes the threshold of nociceptors, magnifying the nociceptive impulses that are transmitted to the central nervous system for pain perception. PGE2 along with bradykinin, can act directly to excite and sensitise peripheral nerve endings, resulting in spontaneous pain and increased pain sensation. Of these mediators, PGs are especially the most important in sensitising the peripheral and neurons to local stimuli. PGs are also synthetized in the spinal cord and probably at higher brain centre in response to noxious stimuli.

2.4 Corticosteroids as anti-inflammatory and pain relief adjuvant

Adjuvant pain medications should be considered in all stage of pain ladder as recommended by World Health Organization (WHO). Steroids in particular, is a useful adjuvant therapy (Vyvey, 2010). Endogenous steroids can be divided into four groups; corticosteroids (glucocorticosetroids and mineralocorticosteroids), progestogens, androgens and estrogens. Glucocorticosteroids are produced by adrenal cortex and have a wide range of actions. They have the properties of anti-inflammatory, reduction of vascular permeability, potency of sodium retention, immunosuppression as well as

pituitary-hypothalamic-adrenal axis suppression. The possible role of steroids on every step of nociception has been raised even though the exact mechanism remains unclear. It has been shown that steroids cause reduction in inflammation following tissue injury by decreasing nociceptors activation and thus, diminish pain intensity. It has been suggested that steroids decrease the pathological electrical activity of the damage neurons. Corticosteroids now are considered as an effective strategy against inflammatory pain.

It is believed that most of glucocorticoids effects on cells are mediated via the glucocorticoid receptors (GR). GR are expressed in almost every type of cells although the density of the receptors may differ from cell to cell. Entry of glucocorticoids into the cell and subsequent binding to the ligand on the receptor, leads to conformational changes in the receptor, forming receptor-steroids (RS) complex (Newton, 2000). The complex is then translocated to the cell nucleus and acts as transcription factor for specific genes to either stimulate or inhibit their expression. It is at this cellular level in which regulatory effects of immune system, including effects on cytokines, are accomplished. Suppression of each stage of the inflammatory response appears to be the major action of the glucocorticoids. Glucocorticoids cause a decrease in capillary dilatation, reduce leukocytes migration and phagocytosis, decrease in the total number of circulating white blood cells and inhibition of formation of granulation tissue by retarding fibroblast proliferation and collagen synthesis. One of the major roles of glucocorticoids to reduce inflammatory response is inhibition of vasoactive substance productions such as prostaglandins, leukotrienes, histamine and serotonin. This is achieved by a generalised reduction in the secretion of lipolytic and proteolytic enzymes such as phospholipase (especially phospholipase A2), collagenase and elastase. Inhibition of phospholipase A2 by glucocorticoids through the release of lipocortin, an inhibitory protein, is the first step in the arachidonic acid cascade (Kim & Brar, 2009). As the consequence, there are inhibitions of all subsequent activity by cyclooxygenases and lipoxygenases lead to

reduced productions of all arachidonic acid products such as prostaglandins, prostacyclins, thromboxanes and leukotrienes.

2.5 Corticosteroids in third molar surgery

The use of corticosteroids as an anti-inflammatory agent in dental practice began in the 1950' with administration of hydrocortisone to prevent inflammation in oral surgery (N. K. Kumar, Krishna, & Silpa, 2017). Over the past few decades, corticosteroids administration, either multiple doses or single dose, pre-operative or post-operative, in third molar surgery as pain model have been extensively studied. The idea of using corticosteroids as an anti-inflammatory agent in dentoalveolar surgery started by Kenny in 1954 who suggested usage of corticosteroids to manage the post-operative sequelae. This was soon after Hench and Kendall were awarded the Nobel Prize from their published report on the successful treatment of rheumatoid arthritis with cortisone in 1949. Spies, in 1952 then reported the use of corticosteroids in dental practice for the treatment of temporomandibular joint arthritis. Ross and White, was the first authors to confirm the efficacy of hydrocortisone given orally against placebo-controlled group in third molar surgery, and their work was published in 1958 (Montgomery & Hogg, 1990) and (Ngeow & Lim, 2016).

Ngeow et al (2018), in their review summarised 104 clinical trials starting from year 1958 until 2017. It is believed that more clinical trials are currently being conducted to evaluate the efficacy of corticosteroids to manage the post-operative sequalae following third molar surgery with different routes of administration, effective therapeutic doses and comparison in combining different pre-operative and post-operative anti-inflammatory medications. Vegas-Bustamante et al in 2008, published a prospective, randomised clinical study, evaluating the efficacy of post-operative single dose intramasseteric 40 mg methylprednisolone on 40 subjects. They found that this regime

had significantly reduced the post-operative pain, swelling and trismus. The technique offers a low-cost solution for management of patient discomfort associated with surgical extraction of impacted lower third molar.

Gataa & Nemat in 2009, evaluated 2 different methods of administration of methylprednisolone on 60 subjects in a randomised, placebo-controlled study. Of the 2 study groups, one received oral 10mg methylprednisolone and another group received 10mg methylprednisolone submucosal injection. They noted that there were significant differences between the experimental groups compared to the control group in swelling reduction and pain relief post-operatively but no significance different in reduction of trismus. The difference in management of post-operative complications following two different methods of administration was also significant. They concluded that giving steroids systemically showed superior effects and played a good role in reducing pain and oedema following third molar surgery. They claimed that the method was simple, applicable and easily accepted by patients.

Selvaraj et al performed a randomised clinical trial to compare different routes of administration of methylprednisolone in third molar surgery. The objectives of the study were to compare the efficacy, advantages and disadvantages of the use of pre-operative methylprednisolone injected into masseter muscle versus gluteal muscle. His work was published in 2014. However, in his study there were no significant differences observed in the efficacy of different routes of administration to minimise the post-operative sequalae after surgical removal of impacted third molars. He did conclude that the intrabuccal masseteric injection is more convenient for the surgeon and painless for the patient since it is administered near the surgical area which is already anaesthetised.

In 2010, Kang et al published a comparative study on a large number of subjects, comparing the post-operative symptoms on patients treated with a single pre-operative

dose of 10mg and 20mg prednisolone given orally. They observed that both dosages had no significant impact on the sequalae of surgical removal of impacted third molars. Based on the results, they concluded that oral dosing of prednisolone of 20mg and lower does not appear to provide significant relief of post-operative symptoms.

In 2014, Hafez et al compared different doses of methylprednisolone with 4mg dexamethasone given submucosally to control oedema, trismus and pain after third molar surgery. Both types of corticosteroids showed improvement in facial swelling, trismus reduction and better pain relief after administration of the drugs. Interestingly, they reported that 80mg of methylprednisolone showed superior result in reduction of facial oedema while 40mg methylprednisolone showed better results in trismus reductions. Overall, methylprednisolone group showed superior effect in pain control compared to dexamethasone group. Their findings concurred with that of al-Khateeb et al (1996) which showed methylprednisolone group required less analgesics.

Lim and Ngeow in 2017 compared the efficacy of submucosal injection of 40mg methylprednisolone and 4mg dexamethasone in reducing post-operative sequelae. Although they reported similar effect in reducing post-operative oedema and trismus, they observed a better post-operative pain reduction in methylprednisolone group. Most recent systematic review and meta-analysis published in 2019, conducted by Almeida et al, analysing 17 randomised controlled clinical trials on the effect of the different types of drugs administered, timings and routes of administration post-operative sequelae. It was concluded that the use of corticosteroids had positive effect in pain control, oedema and trismus associated with surgical removal of impacted mandibular third molars.

2.6 Measurement of inflammatory responses after third molar surgery

2.6.1 Facial swelling / oedema

Facial oedema is the most common, distressing post-operative sequelae and almost inevitable following surgery. This sign is usually transient, but always unpleasant because of the resulting disfigurement and dysfunction. Oedema basically occurs when fluid extravasates from either blood vessel or lymphatic channels. In the normal physiological conditions, the amount of fluid filtration at the end of the arterioles equals to the amount of fluid absorbed at the venule ends. The equilibrium of positive net fluid movement outward (filtration) with the negative net fluid movement inward (absorption) is achieved via capillary hydrostatic pressure and oncotic capillary pressure.

In the event of inflammation, there is increase in capillary permeability allowing movements of protein-rich filtrate into the tissue spaces. This leads to reduce in capillary oncotic pressure and increase in the interstitial oncotic pressure, thereby, exacerbating the net filtration pressure. The absorption of fluid also compromised during the inflammatory process due to release of hydrolytic enzymes by phagocytic cells as well as reactive oxygen and nitrogen species that degrade the extracellular matrix components and the anchoring filaments that are attached to the endothelial cells. This process reduces the radial tension on the valve-like overlapping and interdigitating cell membranes at the inter-endothelial junctions in initial lymphatic channels. Leukocyte-mediated disruption of extracellular matrix components also increases interstitial compliance, which allows a large volume of extracellular fluid to be accumulated within the matrix. Fibrillar components formed by collagen fibres in the interstitial space are also disrupted leading to the loss of extracellular matrix capacity to restrain gel matrix from taking up fluid and swelling.

2.6.1.1 Linear measurement

Linear measurement is an easy method of measuring oedema. This is accomplished by marking a few landmark points and the distance between two points is measured. This

can be carried out using a flexible measuring tape or ruler, a black silk thread or dental floss. Precaution should be taken while measuring as to ensure that the measuring tool (either tape, ruler, thread or floss) is laid passively across the measured area and not being stretched.

Laskin's method as explained by Villafuerte-Nuez et al (2013), which is still used by most researchers since it was introduced in 1987, involved performing three measurements. The first line is the distance between the bottom edge of the earlobe to the midpoint of the symphysis. The second line connecting the bottom edge of the earlobe to the external angle of mouth, whereas the third line is the distance measured from the palpebral outboard angle to the gonion point. Some researchers chose to use only 2 out the 3 lines for the assessment of facial swelling as reported by Lim & Ngeow (2017), Warraich et al (2013), Mohammadi et al (2015)and Grossi et al (2007).

2.6.1.2 Calliper

Breytenbach et al (1978) used a pointed external calliper of approximately 15cm in length to measure facial swelling. One of the tips of the calliper is placed on a fixed point intra-orally such as the inter-cuspal fissure of the second molar while another tip is lightly placed on the anterior margin of masseter muscle. The distance between the 2 tips is then measured. A newly designed calliper was introduced by A.Elmorsy et al (2014), is a modified form aimed to suit its application in the oral cavity to measure the cheek thickness. New removable tips at the end of the calliper ends were added to be easily sterilised and has interchangeable characteristic to be used for both right and left side. It has one pointed tip placed in a hole of acrylic splint fabricated pre-operatively, opposite to the distal part of second molar at its cervical line. The other rounded tip is placed on the outer surface of the cheek at the masseter muscle. The arms of the calliper open and

close using a horizontal screw the outer tip not to pit on oedematous tissue, thereby, allowing the dial reading to be taken.

2.6.1.3 Face bow record

The principle of using face bow method was similar to the face bow record used in prosthetic dentistry. This technique was described by Holland et al (1979). Face bow consists of a metal frame with two sliding pointers and a bite fork covered with dental impression compound. The bite fork attached to the frame by an adjustable clamp and patients are instructed to bite on the softened impression compound placed on the bite fork. Upon hardening of the impression compound, the frame is attached to the bite fork by the clamp and adjustment is made so that the sliding pointers are at right angle to the cheek at a point 3cm along a line from the angle of mandible to the angle of mouth and measurement is made from the sliding pointers reading which is incorporated with a millimetre scale.

2.6.1.4 Photography / Stereophotogrammetry

Two types of photography methods can be used for facial measurement. Ghoddousi et al (2007) described that 2D photographs can be taken using digital camera with small white square plastic cards placed over the forehead and on the flap surfaces of right or left cheeks. The camera lens should be perpendicular to the square. The purpose of the card is to be able to express linear measurements as centimetre. Measurement of the facial swelling should be taken from the frontal print rather than lateral print.

Over the years, the use of stereophotogrammetry is becoming increasingly common. This method allows for the objective assessment of facial form are becoming increasingly important for research in dysmorphology, genetics, orthodontics and surgical disciplines. The system is capable of accurately reproducing the surface geometry of the face, and

map realistic colour and texture. However, several factors should be considered in order to achieve optimal performance such as location and positioning of the camera, software installation, calibration, head position and patient's occlusion. Such issues can adversely impact the reliability of data collection and consequently the clinical and research study result. Ghoddusi et al (2007) in his paper explained that the 3D stereophotogrammetry consists of two camera pods and each pod consists of three digital cameras. Two monochromes cameras are synchronised to capture images illuminated by integral projectors and the third colour camera captures the natural photographic appearance of the subject.

2.6.2 Trismus

Trismus comes from the Greek word *"trismos"* which means grating or grinding. In medical term, trismus is defined as a motor disturbance of trigeminal nerve, characterised by spasm of masticatory muscles with difficulty in mouth opening. Following third molar surgery, there is a transient trismus that reaches its peak on the second day post-operative and resolves by the end of one week.

2.6.2.1 Metal ruler

Metal ruler is often used for measuring the mouth opening. It is quite reliable to measure the distance between the upper and lower incisors as the reference points, but Al-Ani et al (2004) claimed that the inaccuracies are quite high due to angulation at which the ruler is held.

2.6.2.2 Willis bite gauge

A device which consists of two metal arms with a 10cm scale. The top arm, which is longer, is at a right angle to the vertical arm. The adjustable arm is parallel to the right-

angle upper arm and can be slide along the length of the vertical arm. The distance between the two arms measures the mouth opening when held against the upper and lower incisal tips.

2.6.2.3 Alma bite gauge

Alma bite gauge is a 'Vernier style' measuring device. The profile of the pointers is designed to locate the incisor teeth. When the recesses of the gauge are positioned against the edges of the incisor teeth, and the recording device is held vertically with the forward face of the tooth against the vertical stop, a record can be made of the mouth opening distance.

2.6.2 Pain

Measurement of pain is difficult due to a complex sensation associated with personal characteristics and experience affected by emotion and health conditions. Pain manifests itself in numerous ways such as functional limitations, emotional symptoms, physical sensations, and behavioural changes. Clinician should carefully choose the pain assessment tool that most closely corresponds to the patient's symptoms and conditions. Assessment of pain is important as it provide information for clinician to implement successful pain management strategies and improve patient physical and psychological functions which indirectly improve the quality of life.

Acute pain or nociceptive pain associated with tissue damage and inflammation is usually short duration, self-limiting, does not involve neural tissue and tend to be more straightforward to quantify. Pain intensity can be measured in patients in a reliable and valid way by recording the self-rating of the sensation on different types of scales. Several self-rating scales can be used for measurement and assessment of pain.

2.6.3.1 Visual analogue scale

Visual Analogue Scale (VAS) consists of a straight line of 10cm length with the endpoints defining extreme limits such as ‘no pain at all’ and ‘pain as bad as it could be’. The patient is asked to mark his pain level on the line between the two endpoints. The distance between the ‘no pain’ end to the respondent’s mark is then measured and recorded as the pain intensity. Caraceni et al. in 2002, agreed that VAS as the most commonly studied pain assessment tool and is often considered as ideal scale because it is continuous and more independent from language than the verbal scale.

2.6.3.2 Graphic rating scale

It is similar to VAS but descriptive terms like ‘mild’, ‘moderate’, ‘severe’ or a numerical scale is added to the scale (Haefeli & Elfering, 2006). In several studies, VAS and GRS have been demonstrated to be sensitive to treatment effects. They were found to correlate positively with other self-reporting measures of pain intensity. In addition, difference in pain intensity measured at two different points of time by VAS represents the real difference in magnitude of pain which seems to be the major advantage of this tool compared to others.

2.6.3.3 Numerical rating scale

In a Numerical Rating Scale (NRS), patients are asked to circle the number between 0 and 10, 0 and 20 or 0 and 100 that fits best to their pain intensity. It consists of a horizontal straight line with the number at the bottom of the line and giving the scale of 0 represents ‘no pain at all’ whereas the upper limit either 10 or 20 or 100 which represent ‘the worst

pain ever possible'. In contrast to the VAS, the numbers themselves are valuable answers. It thus allows only a less-subtle distinction of pain levels compared to VAS, where there are theoretically unlimited number of possible answers. Numerical Rating Scales have shown high correlations with other pain-assessment tools in several studies as reported by Haefeli et al (2006). The feasibility of its use and good compliance have also been proven.

CHAPTER 3: METHODOLOGY

3.1 Sample collection

This study was carried out in the Oral and Maxillofacial Surgery Clinic, Faculty of Dentistry, University of Malaya from August 2017 to February 2019. Participants for this study were recruited on a random basis from patients who were referred to the Oral and Maxillofacial Surgery Clinic, Faculty of Dentistry, University of Malaya for surgical removal of impacted mandibular third molars. This study was conducted with the approval from the Ethical Committee of Faculty of Dentistry, University of Malaya DF OS1708/0030 (P) and was conducted in accordance with the Declaration of Helsinki. Patients were given full information about the study in both written and verbal forms prior to obtaining their consent. Enrolment into this study was purely voluntary.

Participants of this study had to be healthy without any co-morbidities (American Society of Anesthesiology 1 [ASA-1]). Cases that were included were those with impacted third molar (Pell and Gregory Class II or Position B) requiring flap raising and osteotomy.

Exclusion criteria were as follow:

- significant medical problems
- smoking
- allergic or history of adverse effects with methylprednisolone, amoxicillin, ibuprofen or paracetamol
- signs of acute pericoronitis
- contraindicated for test drugs
- chronic use of medications that would obscure assessment of inflammatory response

- pregnant or lactating women
- patients who are unwilling to undergo data collection procedures
- surgery of more than 45 minutes (from the time first incision is made to the last suture placed)
- patient with missing either upper or lower central incisors

Participants were divided into three groups. They were required to pick a number from a sealed box to represent a study group (1=Post-operative ibuprofen (Control), 2=Pre-operative submucosal methylprednisolone and post-operative ibuprofen, 3= Pre-operative submucosal methylprednisolone and post-operative paracetamol). The number was then passed to a colleague who will prepare both pre-operative and post-operative medications. This colleague will then give submucosal injections and instructions on post-operative medications in the absence of the surgeon. The surgeon was blinded of the medications given throughout the studies.

3.2 Surgical Protocol

Prior to the surgery, dental panoramic radiograph was taken for every patient to determine the degree of impaction of mandibular third molar according to Pell and Gregory classification. Surgeries were performed by the same surgeon under local anesthesia. The surgeon had more than 5 years of experience in third molar surgery.

Prior to the surgery, patients were required to gargle with 012% of Chlorhexidine mouthwash (ORADEX®) for one minute. Ipsilateral inferior alveolar nerve, lingual nerve and long buccal nerve blocks were given using Mepivacaine 2% with 1:100,000

Adrenaline. Upon achieving anaesthesia, another colleague would then give submucosal injection of Methylprednisolone to patient in Group 1 and Group 2. No submucosal injection was given to Group 3. During this time, the surgeon was not present in the surgery room.

Ten minutes later, a standard Ward's incision was made from the distal surface of the mandibular second molar extending to the distal of the mandibular third molar with mesial and distal relieving incision. The trapezoid flap was then raised with a Howarth's periosteal elevator. The flap was carefully protected with a Bowdler-Henry flap retractor. Gutter was then made until the level of cemento-enamel junction of the third molar with a round surgical bur. The tooth was sectioned (if necessary) with a straight fissure surgical bur and removed. Any rough bone margin was smoothened, and surgical site was irrigated with normal saline. Haemostasis was achieved prior to closure. Flap was then reapproximated and sutured with resorbable sutures. The mesial relieving incision was left un-sutured.

The surgical procedure was timed from the first incision made to the last suture placed. Any surgery longer than 45 minutes was excluded from this study. Post operatively, patient was prescribed with antibiotic (Amoxicillin 250mg every 8 hours for five days, in case of allergic to Amoxicillin, Erythromycin 250mg every 8 hours for five days were given) and analgesic (according to the respective study group; Ibuprofen 400mg every 8 hours for five days in Group 1 and Group 3, Paracetamol 1000mg every 6 hours for five days in Group 2). In addition to that, Tramadol 50mg tablets were provided as a rescue medicine in case the analgesics provided were not adequate to relieve the pain.

3.3 Data collection

Assessments were made pre-operatively and on post-operative day 1, 2 and 7. Pre-operative baseline facial measurements and width of mouth opening were taken. Facial swelling measurements were taken as the sum of length of two lines along the pre-determined facial reference points from the outer corner of the eye to angle of mandible and tragus of the ear to corner of the mouth. Facial measurement was measured using a tape measure. The percentage of facial swelling was then calculated based on the differences between baseline measurements with measurements taken on the 4 days of study.

Trismus was calculated as the changes in the width of mouth opening (maximum interincisal distance) between pre-operative and post-operative day 1, 2 and 7. This distance was measured using a metal ruler.

Pain was evaluated and recorded on post-operative 1,2, 3, 4, 5, 6, 8, 12, 24 hours and on Day 2 and 7 using a 10cm-long graphic VAS scale. Pain relief score was also recorded during the same time frame. This Pain relief score comprised of 4-point categorical verbal scale i.e 0=none, 1=slight, 2=moderate, 3=completely. Amount of analgesic and rescue medicine consumed throughout the same period was also recorded.

3.4 Data analysis

Data obtained were analysed using Statistical Package for Social Sciences (SPSS) software version 24.0. Descriptive analysis data including mean, median, maximum and minimum values were computed.

Data from the three study groups were analysed using repeated measure analysis of variance (ANOVA). The paired groups were further compared by performing Post Hoc

(Tukey's) test. Significant value was set at $P<0.05$ level. Pearson correlation was also computed to investigate relationship between VAS score with number of rescue medication, facial swelling and trismus. A P-value <0.05 was set as significant.

CHAPTER 4: RESULT

4.1 General profile

A total 60 patients were enrolled in this study. Out of these 60 patients, two were excluded from analysis. One of the patients had allergic reaction to Ibuprofen while another patient failed to attend the follow up appointment. The age of these patients ranged from 19 to 45 years old with a mean (SD) of 25.67 (4.91) years old. Most of the patients enrolled were Chinese (n=28, 48.3%), followed by Malay (n=26, 44.8%) and the least enrolled race group was Indian (n=4, 6.9%). It was also observed that more female patients (n=32, 55.2%) were enrolled in this study compared to male patients (n=26, 44.8%). There was no significance difference in term of age, tooth, gender and ethnicity as presented in the demographic characteristic table below. All patients were treated in less than 45 minutes, with the mean surgery time (SD) of 34.66 minutes (4.02) and it was found that there was no significant difference in the duration of the surgery between the three groups. (Table 4.1a)

Table 4.1a: Demographic characteristics and clinical data of participants

Groups		MP + Ibuprofen	MP + PCM	Control	Total	P-value
Gender	Male	11	7	8	26	0.455
	Female	9	13	10	32	
Ethnicity	Malay	7	10	9	26	0.736
	Chinese	12	8	8	28	
	Indian	1	2	1	4	
Tooth	38	9	10	10	29	0.810
	48	11	10	8	29	
Age (mean)		25.25 ± 4.5	26.45 ± 4.7	25.28 ± 5.7	25.67 ± 4.91	0.305
Surgery time (mean)		35.35 ± 3.7	34.00 ± 4.5	34.61 ± 3.9	34.66 ± 4.02	0.905

4.2 Pain

Visual analogue scale (VAS) was used as a tool to measure post-operative pain. The mean, VAS score is shown in Table 4.2a. Following Post Hoc Test (Tukey's), groups that received pre-operative submucosal Methylprednisolone recorded significantly lower pain score compared to control group from post-operative 4 hours to 8 hours. Repeated measure was utilised to analyse the time effect on pain. Pain score for control group peaked at post-operative 8 hours while both test groups peaked at post-operative 3 hours at lower pain score.

Table 4.2a: Mean post-operative pain score

Post-operative period	MP + Ibuprofen		MP + PCM		Control	
	Mean (SD)	Min - Max	Mean (SD)	Min - Max	Mean (SD)	Min - Max
H1	1.6 (±2.2)	0 - 7	2.3 (±1.9)	0 - 7	1.3 (±1.5)	0 – 5
H2	2.4 (±2.3)	0 - 6	2.9 (±2.2)	0 - 8	2.5 (± 2.1)	0 – 8
H3	2.6 (±1.9)	0 - 6	3.3 (±2.5)	0 - 8	3.1 (±1.6)	0 – 7
H4	2.3 (±1.4)	0 - 4	2.8 (±2.3)	0 - 6	3.8 (±1.8)	0 – 8
H5	2.3 (±1.6)	0 - 6	2.6 (±2.2)	0 - 6	3.6 (±1.5)	2 – 7
H6	2.3 (±1.6)	0 - 6	2.3 (±1.9)	0 - 7	3.8 (±1.8)	2 – 8
H7	2.0 (±1.5)	0 - 6	2.2 (±1.7)	0 - 6	4.2 (±1.9)	1 – 8
H8	2.2 (±1.3)	0 - 4	1.9 (±1.6)	0 - 6	4.4 (±2.0)	1 – 8
H12	1.7(±1.5)	0 - 5	1.9 (±1.6)	0 - 6	2.8 (±1.7)	0 – 6
H24	1.2 (±1.1)	0 - 4	1.0 (±0.9)	0 - 3	2.7 (±1.7)	1 – 6
D2	0.7 (±0.9)	0 - 2	0.8 (±1.0)	0 - 3	1.8 (±1.8)	0 – 7
D7	0.2 (±0.5)	0 - 2	0.3 (±0.6)	0 - 2	0.8 (±1.2)	0 – 4

Fig 4.2a Mean post-operative VAS score

Amount and frequency of rescue analgesic consumption is shown in Table 4.2b. Pearson correlation coefficient shows a moderate, positive correlation between the number of rescue analgesic consumed by patients of different groups (r= 0.401, p= 0.284).

Table 4.2b. Frequency and amount of rescue analgesic taken

No. of Recue Analgesic Taken	MP + Ibuprofen	MP + PCM	Control	Total
1	1	2	2	5
2	0	1	2	3
>3	0	0	1	1
Total (%)	1 (1.7)	3 (5.2)	5 (8.6)	9 (15.5)

4.3 Facial Swelling

Two linear lines, from bottom edge of earlobe to ipsilateral external angle of mouth and from lateral canthus of the eye to ipsilateral angle of mandible, were measured and

summed up to obtain measurement for facial swelling. Mean percentage of changes of facial swelling is shown in Table 4.3a and Figure 4.3a.

Table 4.3a: Mean percentage of post-operative facial swelling

Groups		POD 1	POD 2	POD7
MP + Ibuprofen	Mean (SD)	3.0	2.8	0.5
	Min-Max	0.4 - 9.5	0.9 – 8.4	0 – 3.4
MP + PCM	Mean (SD)	4.2	4.8	0.9
	Min-Max	1.0 – 8.9	0.5 -17.1	0 – 5.4
Control	Mean (SD)	4.9	5.0	1.5
	Min-Max	1.5 – 10.3	0.9 – 14.4	0 – 14.4

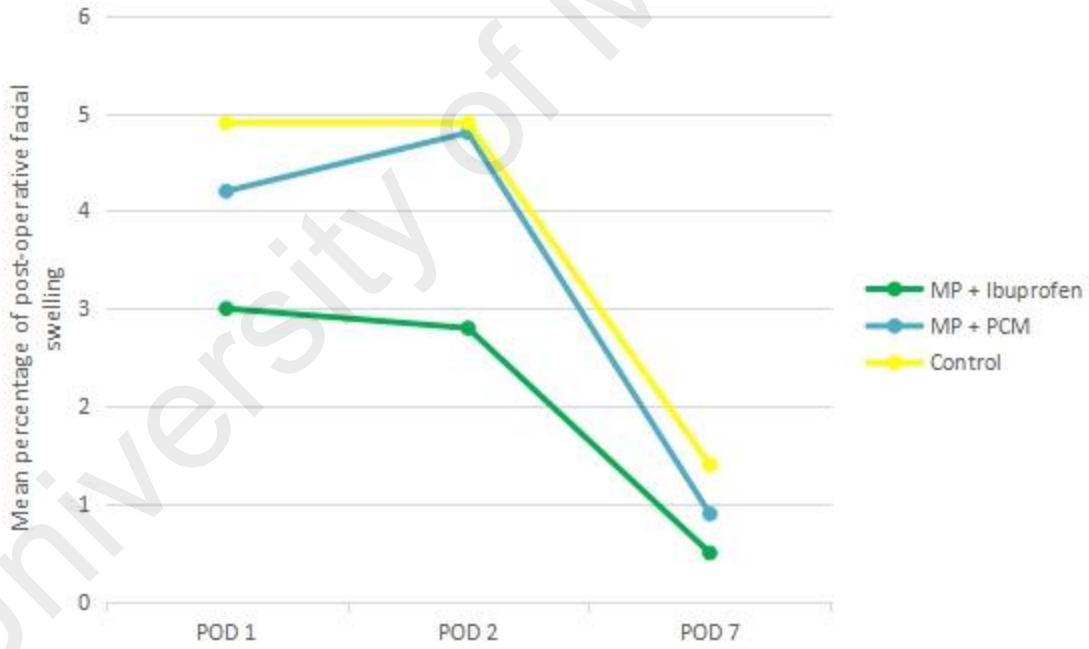

Fig. 4.3a: Mean percentage of post-operative facial swelling

Facial swelling peaks on post-operative Day 1 for control group and group with combination of methylprednisolone and paracetamol. However, another test group, combination of methylprednisolone and ibuprofen, facial swelling peaks on post-

operative Day 2. Post Hoc Test (Tukey's) revealed no significant difference in facial swelling among all the three groups.

Pearson correlation coefficient was computed to see the relation between patients' recorded pain score and facial swelling. It was noted that there was a weak, positive correlation between pain score and facial swelling on all the 3 studied days (POD1 r= 0.252, p= 0.056, POD2 r = 0.109, p= 0.415, POD7 r =-0.084, p= 0.0531).

4.4 Trismus

Trismus was assessed by measuring the distance between incisal edge of upper and lower central incisors using a metal ruler. Mean percentage of reduction of mouth opening throughout the study days is shown in Table 4.4a and Figure 4.4a.

Table 4.4a: Mean percentage of reduction of mouth opening

Groups		POD 1	POD 2	POD7
MP + Ibuprofen	Mean (SD)	-27.7	-21.5	-6.0
	Min-Max	-54.3 - -2.4	-49.1 - 0	-33.3 - 0
MP + PCM	Mean (SD)	-34.1	-31.2	-11.8
	Min-Max	-58.7 - -5.6	-54.2 - 0	-41.7 - 0
Control	Mean (SD)	-36.9	-28.3	-10.2
	Min-Max	-57.1 - -2.8	-51.4 - -4.1	-46.7 - 0

Note: Baseline was set at "0". Any reduction in mouth opening is reported in negative

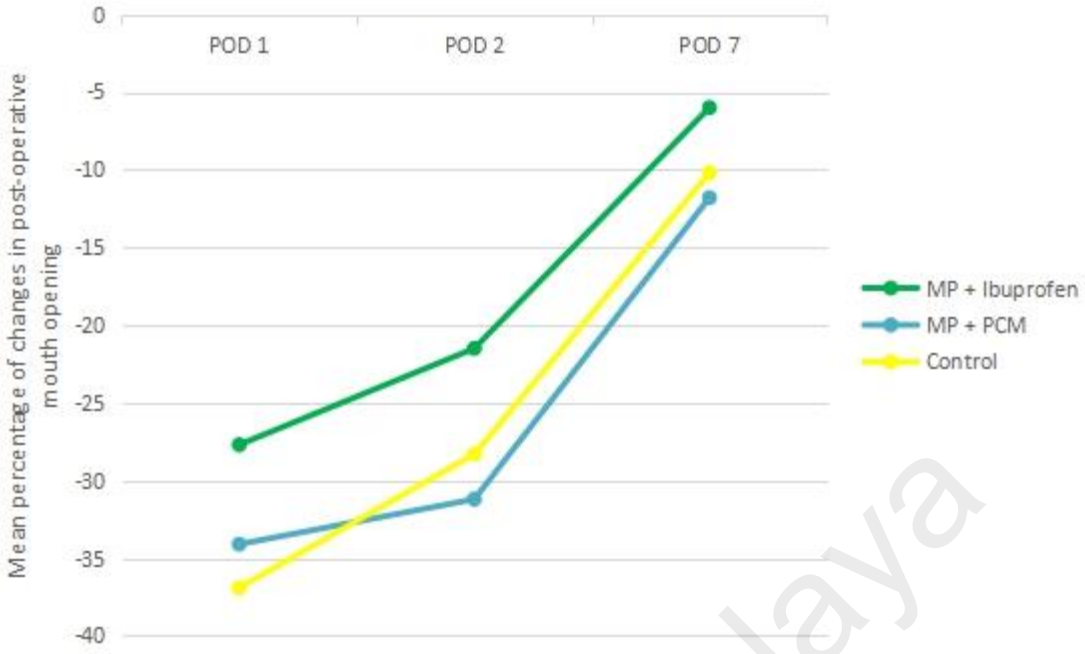

Fig. 4.4a: Mean percentage of changes in post-operative mouth opening

All study groups show similar trend of most reduction of mouth opening on post-operative Day 1 and progressively improve on post-operative Day 7. Both methylprednisolone and ibuprofen group and control group show a steep improvement from post-operative Day 1 to post-operative Day 2. The differences among the three groups were not statistically significant.

Relationship between changes in mouth opening and pain score was assessed using Pearson correlation coefficient test. There was negative correlation between the two variables on all the 3 studied days (POD1 r = -0.195, p-value = 0.143, POD2 r = -0.166, p-value =0. 212, POD7 r = -0.133, p-value = 0.321).

CHAPTER 5: DISCUSSION

The phenomenon of inflammation after surgical removal of impacted mandibular third molars plays a vital role in post-operative healing. As common as the procedure is performed in dentistry, so does the post-operative sequelae and complications. Common sequelae of mandibular third molar surgery are swelling, trismus and pain. The degree and severity of inflammatory consequences after the surgery depend on many factors such as individual physiological response to the procedure, the degree of impaction, duration of the surgery and amount of tissue trauma or tissue manipulation during the surgery.

Pain following surgical removal of impacted third molar has been the focus of previous many studies. This is mainly due to its effect on patient's quality of life. Nonetheless, pain is the most difficult and challenging to treat. This is because body responds to pain through numerous and interconnected physiological processes; sympathetic nervous system, neuro-endocrine system, immune system as well as emotion. The complexity of pain makes it more difficult to manage than other post-operative sequelae.

Various methods had been described and suggested to reduce these post-operative sequelae either pharmacologically (eg: corticosteroids, hyaluronic acid, serropeptidase) and non-pharmacologically (eg: cold pack, corrugated drain). There is a broad discussion about the best drug to minimise post-operative discomfort, and corticosteroids had been most extensively studied drug due to its efficacy to control inflammatory complications. Corticosteroids versatility is appreciated as it can be administered at different timing i.e pre-operative, intra-operative and post-operative, as well as via different routes i.e intravenous, intramuscular, submucosal and endo-alveolar. This study was designed to compare the effect of combination pre-operative submucosal dexamethasone with different post-operative analgesics in pain control following surgical removal of impacted third molars.

5.1 Rationale of study

It is worth highlighting that among the studies on the use of corticosteroids to control the post-operative inflammatory sequelae, very few had combined pre-operative corticosteroids with different post-operative pain medications. Most of them focused on the administration of different agents and/or different doses and/or different routes administration. For more than 40 years, corticosteroids have been used in the attempt to minimise or prevent the post-operative complications and many studies have reported on successful outcomes of corticosteroids to significantly reduce pain, swelling and trismus.

Considerations in choosing the therapeutic regimen of corticosteroids in third molar surgery should include; the type of steroids, the dose, the route of administration, single of multiple dosing and the timing of the administration relative to surgical procedure. The best suited agent should be used in short-term, provide high-dose therapy with extended biological activity but possesses minimal mineralocorticoid activity. Methylprednisolone meets the criteria as suggested by Montgomery et al (1990), in which it is five times more potent than cortisone, moderate duration of activity with its half-life around 180 minutes and its duration of action spans from 24-36 hours. Furthermore, methylprednisolone also has the least mineralocorticoids activity, thus, less tendency to induce sodium and water retention.

Ibuprofen and Paracetamol were as post-operative pain medications based on their different anti-inflammatory properties. Paracetamol is the most widely used over-the-counter prescribed analgesic, used to treat mild to moderate pain and generally considered to be safer than other commonly used analgesics (Roberts et al., 2016). Its analgesic property is of unknown mechanism although recent studies demonstrated that

paracetamol causes weak inhibition of prostaglandin production. Ibuprofen, a member of proprionic acid derivatives, has been rated as the safest conventional NSAIDs by spontaneous adverse drug reaction reporting system (SADRRS) in UK (Bushra & Aslam, 2010). It is one of the most common prescribed analgesics by dentist worldwide. A low dose of ibuprofen is as effective as aspirin to treat mild to moderate pain such as dental pain.

5.2 Pain

Pain is measured using VAS score. Generally, patient starts to experience pain two hours post-operation. The pain increases in intensity until post-operative eight hour and gradually reduces until post-operative day seven. Acute pain following surgical incision initiates a series of neurochemical reactions at the site of injury and initiates a cascade of changes leading to sensitisation of in the central nervous system. Localised production of inflammatory mediators might not be the sole cause of post-operative pain. Therefore, administration of post-operative analgesics alone might not be helpful to reduce pain as we assumed that common drugs such as NSAIDs and Acetaminophen acts primarily peripherally at site of inflammation.

Some authors also have attributed the pain to be intense due to soft tissue swelling (Klongnoi et al, 2012 and Maung Maung et al, 2016). In our study, there was a weak relationship between facial swelling and pain, and it was not statistically significant. This explained that central sensitisation of pain following the surgery is equally important in post-operative pain. Afferent signals from nociceptors can be amplified or attenuated along the pathways to central nervous system and central sensitisation begins as signals reach the dorsal horn of spinal cord which is the key area of the process. Pain persists even though at lower amplitude despite inhibition of prostanoids production already occur at the peripheral site.

In our study, there was significant differences between the methylprednisolone groups and control group. Our finding concurred with that reported by Junaid Ashraf et al (2014) and Rishi et al (2018). Many authors tried to explain this finding. It was suggested that due to the presence of glucocorticoid receptors at the spinal cord and brain tissues, they act as transcriptions factors for specific genes, stimulating or inhibiting its expression at the cellular level. Consequently, there is a change in gene expression and protein synthesis and becomes apparent after few hours on its clinical impact. This will further inhibit the formations of pro-inflammatory cytokines and mediators, thus regulate the transduction and transmission of pain signal in central nervous system and this may be the reason for groups with methylprednisolone to have lower pain score.

On post-operative 4 hour to post-operative 8 hour, there were significant difference between methylprednisolone groups and control group. This finding concurs with report by Kaur et al (2011), who reported of significant pain reduction up to post-operative 24 hour. This was attributed from the effect of methylprednisolone reaching its therapeutic level. On post-operative day two onwards, there was no significant difference observed between methylprednisolone groups and control group. This finding was also like that reported by Kaur et al (2011) although in their study methylprednisolone was given via intra-masseteric injection post-operatively.

It is also important to note that the relationship between post-operative analgesics requirement with patients' pain score was difficult to evaluate as two different post-operative analgesics was given with different doses and frequencies. With regards to the number of rescue medications taken, control group showed highest number of consumptions compared to methylprednisolone groups. Only one participant in the methylprednisolone and ibuprofen group took rescue medication throughout the study compared to five participants in control group and three participants in

methylprednisolone and paracetamol group. This implies that combination of methylprednisolone and ibuprofen provides good post-operative pain control. Combining methylprednisolone with either ibuprofen or paracetamol reduces the need of consuming rescue medication. On post-operative day 7, pain score was approaching zero and almost all patient had stopped consuming analgesics. This renders no significant different among all three groups.

5.3 Swelling

Various methods have been used to measure facial swelling. It should be noted that facial swelling occurs in three dimensions. Although many authors preferred the use of computed tomography (CT) and magnetic resonance imaging (MRI) to make precise measurement of facial swelling, however they are invasive, time consuming and expensive. In our study, a linear measurement using flexible ruler was used to measure facial swelling as it as easy, inexpensive and relatively reproducible. Two lines was used in the evaluation of facial swelling in our study; linear measurement of vertical line (outer canthus of ipsilateral eye to ipsilateral angle of mandible) and horizontal line (ipsilateral tragus to ipsilateral corner of mouth).

Generally, in our study there was no significant effect of pre-operative submucosal methylprednisolone on post-operative facial swelling throughout the evaluation period. This finding concurred with that reported by Selvaraj et al (2014). Al-Khateeb et al (1996) studied on the effect of pre-operative submucosal methylprednisolone on facial swelling also found that there was no significant difference between the groups received steroids and control group. They reported that facial swelling increased in size on post-operative day one and started to reduce in size on the following day.

As swelling mainly happens at the site of surgery, no central activity of any drugs is of importance. Molecular studies had shown that corticosteroids can reduce inflammatory mediators via a few pathways. First is the activation of annexin I which inhibits phospholipase A2. The latter inhibits the breakdown of phospholipids into arachidonic acid and therefore inhibits formation of prostanoids. Second is activation of mitogen-activated protein kinase (MAPK) phosphatase 1, which inhibits MAPK, a transcellular transducer important in activating phospholipase A2. Glucocorticoids also can suppress cyclooxygenase 2 by its direct inhibitory effect on nuclear factor ƙB (NF-ƙB). Inhibition of production of these inflammatory mediators leads to reduction of vasodilation and vascular permeability. As a result, less transudation and therefore less oedema.

However, it was observed on post-operative day two that group given methylprednisolone and paracetamol showed an increased in facial swelling compared to post-operative day one. This phenomenon was not observed in the other two groups. This increased of facial swelling on post-operative day two is known as rebound swelling. This phenomenon occurs with administration of single dose corticosteroids. This was not observed in methylprednisolone and ibuprofen group probably due to the potent anti-inflammatory effect of ibuprofen, which continued to suppress the inflammatory process. Alexander & Throndson et al (2000) stated that rebound swelling can occur if the duration of corticosteroids use is inadequate. They suggested to maintain the level of short duration steroids formulation for more than one day.

Our finding also supported the lack of anti-inflammatory property of paracetamol compared to ibuprofen. This was observed in their effect on post-operative swelling and trismus. Group with paracetamol showed less reduction in facial swelling compared to other groups. Even control group that was not given pre-operative methylprednisolone had better improvement in mouth opening throughout the studied days. Due to its lack of

anti-inflammatory property, it was observed that there was a rebound swelling on post-operative Day 2 in methylprednisolone and paracetamol group. Anti-inflammatory effect of methylprednisolone was not able to be sustained by paracetamol, in contrast to that observed in methylprednisolone and ibuprofen group.

There is no significant difference in facial swelling measured at post-operative day seven. This finding concurred with that reported by Selvaraj et al (2014), Choudrand-Lara et al (2013) and Acham et al (2013). Facial swelling was shown to almost reach the baseline by post-operative Day 7 following the surgery.

5.4 Trismus

Trismus, one of the sequelae following surgical removal of impacted third molars can be caused by several factors such as pain, hematoma formation, oedema as well as muscle injury during the surgery. Measurement of trismus is relatively more consistent in contrast to measurement of facial swelling as all authors measured the inter-incisal distance. We found that trismus is inversely related to the pain which means that the more severe the pain, the less the mouth opening. Previous study had shown that submucosal injection of corticosteroids greatly reduced post-operative trismus. This was observed in post-operative Day 1 in our study.

Mean percentage of changes in mouth opening, which represented trismus in this study showed a progressive improving pattern throughout the assessment period. Worst mouth opening was recorded at post-operative Day 1 in all groups. This finding was similar with that reported by Hafez et al (2014) and N.Kaur et al (2014). Trismus improved in all groups started from post-operative day two until day seven with patients in the control group showed the least improvement as compared to the methylprednisolone groups at

all three assessment days. However, it was not statistically significant. The same finding has been reported by Gaata et al (2009).

Previous studies by Mico-Lloren et al (2006), Vegas-Bustamante et al (2008), Kaur et al (2011), Acham and Klamfl et al (2013), Ashraf et al (2014), Hafez et al (2014) and N. K. Kumar et al (2017) reported that the use of methylprednisolone significantly reduce the amplitude of trismus after surgery. Although the changes in our study is not statistically significant, the trend of trismus throughout the studied days was similar. These variations of finding could be attributed to the other factors such as injury to the temporomandibular joint, hematoma formation following inferior alveolar nerve bock and injury to the masticatory muscles during the surgery especially upon reflection of flap.

5.5 Healing and complication

Out of 60 patients enrolled in this study, one patient reported of allergic to the Ibuprofen. Patient reported of having periorbital swelling and urticaria following ingestion of the medications. Patient was advised to stop taking the medication and was prescribed with chlorpheniramine. Periorbital swelling and urticaria subsided within 24 hours after antihistamine therapy. No other serious complications reported, no anaphylaxis and no admission required. The incidence of hypersensitivity or allergic to NSAID is relatively low. Previous study on self-reporting allergy to NSAIDs suggest that the incidence is as low as 1.9% to 3.5% and the risk increased with the increased in dose and duration of usage (Blumenthal et al., 2017).

In this study, no wound healing impairment was noted during post-operative day seven. The healing was considered satisfactory when the socket was pain free and the healing was by primary intention, or, if the healing was by secondary intention, when

socket self-cleansing and did not require occlusive dressing as well as absence of infections (Herrera-Briones et al, 2013). Studies reported that single dose of corticosteroids did not impair wound healing (Gersema and Baker, 1992).

5.6 Limitation of study

Main issue prior to embarking on this study was funding. As the price of methylprednisolone acetate (Depo Medrol®, Pfizer) was expensive, institution research committee had queried the significant of carrying out this study. The appealing process took almost 1 year before the proposed research funding was approved.

Recruitment of participants in a period of one year proved to be a challenge together with initial restriction of fund prior to starting the research. This was made worse when potential participants were informed that they might be given steroids and the concern of possible adverse reactions from the medications. This had led to many potential participants refusing to take part in this research.

Consumption of analgesics by participants was difficult to control. Participants might have consumed analgesic "prophylactically" in view of fear of pain developing, despite repeated reminder by researcher to consumed only when in pain during every assessment visit. There were possibilities that some participants may have consumed other analgesics but was not reported to the researcher. Exclusion of these participants was difficult as patients might not willingly inform the researcher of this fact.

Limited previous studies comparing single pre-operative corticosteroids with different post-operative analgesics had also posed a problem in obtaining relevant references. Most of the studies conducted were either comparing different types, doses or routes of corticosteroids. This was also the reason behind the conduct of this study.

CHAPTER 6: CONCLUSION

6.1 Conclusion

In summary, patients given pre-operative submucosal injection of 40mg methylprednisolone before surgical removal of impacted third molar did show significant pain control post-operatively. This beneficial effect was seen mostly at day one post-operative. As for the reduction of facial swelling and trismus, no significant differences were observed. Although no significant difference was observed in reduction of facial swelling, group with combination pre-operative methylprednisolone and post-operative paracetamol showed rebound phenomenon on post-operative Day 2. Control group also showed the least in improvement of mouth opening at all three assessment days though the difference was not statistically significant. Single dose of pre-operative submucosal injection of methylprednisolone did not have any adverse effect on the healing of surgical site. Healing was uneventful for all patients in this study.

6.2 Recommendation

Although this study proved that the pre-operative submucosal injection of methylprednisolone was beneficial for pain control following surgical removal of impacted third molar, its effect on post-operative swelling and trismus is still not very convincing. Future study using comparing different doses or routes of administration will determine the best therapeutic dose and route to reduce post-operative discomfort. We would also like to suggest the use of different post-operative analgesics to include opioids in future study to determine analgesic and anti-inflammatory effects of corticosteroids in third molar surgery.

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