Effect of Intravenous Paracetamol for Post operative pain relief after Tonsillectomy

A study of 70 cases

Dissertation

Submitted in partial fulfillment of university regulations for the award of

M.D. DEGREE EXAMINATION

BRANCH X – ANAESTHESIOLOGY

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

APRIL 2011

CERTIFICATE

This is to certify that the Dissertation "**Effect of Intravenous Paracetamol for Post operative pain relief after Tonsillectomy**" presented herein by **Dr. K. Paul Praveen** is an original work done in the Department of Anaesthesiology, Tirunelveli Medical College Hospital, Tirunelveli for the award of Degree of M.D. (Branch X) Anesthesiology under my guidance and supervision during the academic period of 2008-2011.

The Dean

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This is to certify that the INSTITUTIONAL ETHICAL COMMITTEE of TIRUNELVELI MEDICAL COLLEGE AND HOSPITAL, TIRUNELVELI-11 has unanimously approved the dissertation titled POST OPERATIVE ANALGESIA AFTER INTRAVENOUS PARACETAMOL FOR 20 CASES UNDERGOING TONSILLEETOMY AND COMPARE IT WITH 20 CASES WITHOUT HAVING INTRAVENOUS PARACETAMOL AS POST OPERATIVE PAIN RELIEF by DR.PAUL PRAVEEN,MD (ANAE) II YEAR student, TIRUNELVELI MEDICAL COLLEGE, TIRUNELVELI-11 in its meeting held on 09.10.2009.

TIRUNELVELI

13 .10.2009.

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DECLARATION

I, **DR. K.PAUL PRAVEEN** declare that the dissertation titled "**Effect of Intravenous Paracetamol for Post operative pain relief after Tonsillectomy"** has been prepared by me.

This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D., Branch X (ANAESTHESIOLOGY) Examination to be held in April 2011.

Place : Tirunelveli

Date : **DR.K.PAUL PRAVEEN**

ACKNOWLEDGEMENT

I wish to express my sincere thanks to **The Dean**, Tirunelveli Medical College, Tirunelveli for having kindly permitted me to utilize the hospital facilities.

I have great pleasure in expressing my deep sense of gratitude to **Prof. M. KANNAN M.D., D.A.,** Professor and Head of the Dept. Anaesthesiology, Tirunelveli Medical College, Tirunelveli for his kind encouragement and valuable guidance during the period of this study, without which this dissertation would not have materialized.

I would like to place on record my indebtedness to my **Prof. A. THAVAMANI. M.D., D.A.,** Professor of Anaesthesiology, Tirunelveli Medical College, Tirunelveli for his whole hearted help and support in doing this study.

I express my profound thanks to **Prof. A. BALAKRISHNAN. M.D.,** Associate professor of Anaesthesiology, Tirunelveli Medical College for his valuable help in carrying out this study.

I also express my sincere thanks to **Prof .S. SURESH KUMAR. M.S., D.L.O.,** Professor and Head of the Dept. ENT, Tirunelveli Medical College, for granting me permission to perform my study in ENT patients.

I am extremely thankful to **Dr. R. SELVARAJ. M.D.**, Senior Assistant professor of Anaesthesiology, Tirunelveli Medical College, for his sagacious advice and appropriate guidance to complete this study.

I am extremely thankful to **Dr. G. VIJAY ANAND M.D.**, Assistant professor of Anaesthesiology Tirunelveli Medical College, for all the help he has rendered and the time he has spent in making me complete this study.

I thank all the Assistant Professors and Senior residents for their able help, support and supervision during the course of the study.

I extend my thanks to **Mr. Arumugam, M.Sc.,** the Statistician, for his able analysis of the data.

I thank all the patients included in the study and their relatives, for their whole hearted co-operation in spite of their illness.

CONTENTS

LIST OF ABBREVIATIONS

ASA	-	American Society of Anesthesiologists
Ca^{2+}	-	Calcium
CNS	-	Central Nervous System
COX	-	Cyclooxygenase
ECG	-	Electrocardiography
ENT	-	Ear Nose Throat
ETT	-	Endotracheal tube
IM	-	Intramuscular
IV	-	Intra Venous
K+	-	Pottasium
MAP	-	Mean arterial pressure
Mg^{2+}	-	Magnesium
Na+	-	Sodium
NIBP	-	Non Invasive blood pressure
NMDA	-	N- methyl D- aspartate
N_2O	-	Nitrous Oxide
NSAIDS	-	Non steroidal anti inflammatory drugs
O_2	-	Oxygen
PACU	-	Post anesthesia care unit
PONV	-	Post-operative nausea and vomiting
%	-	Percentage
Spo2	-	Arterial Oxygen saturation
SD	-	Standard deviation
VAPS .	-	Visual analog pain scale

INTRODUCTION

Tonsillectomy is one of the commonest surgical procedures performed in the field of otorhinolaryngology. The most common and distressing symptoms, which follow anaesthesia and surgery, are pain and emesis[1]. The provision of adequate analgesia after tonsillectomy presents the anaesthesiologist with difficulties, as this is a painful procedure and may be associated with significant bleeding into the airway[2]. As evidence continues to accumulate concerning the role of central sensitisation in post operative pain, many researchers have followed methods to prevent central neuropathic changes from occurring, through the utilization of pre-emptive analgesic techniques. Effective preventive analgesic technique may not only be useful in reducing the acute pain, but also chronic post surgical pain and disabilities. Paracetamol is an effective analgesic and an antipyretic agent[3, 4]. The efficiency and tolerability for intravenous Paracetamol are well established. It has a favourable safety profile and it is the most commonly prescribed drug for the treatment of mild to moderate pain. The objective of the present study is to evaluate the post operative analgesia, the haemodynamic profile and the side effects of IV Paracetamol.

AIM OF THE STUDY

- To evaluate the efficacy of Intravenous Paracetamol as a pre-emptive analgesic in relieving the post operative pain.
- To study the hemodynamic variables during the post-operative period.
- To establish the safety of Intravenous paracetamol in patients.

REVIEW OF LITERATURE

Atef A et al[5] performed a prospective placebo-controlled study to evaluate the analgesic efficacy and safety of intravenous paracetamol undergoing elective standard bipolar diathermy tonsillectomy and concluded that intravenous paracetamol significantly reduced pethidine consumption over a 24 hour period. The worst pain after surgery was also more severe in the placebo group than that in the paracetamol group. There was no significant difference between groups in the incidence of adverse events. Intravenous paracetamol administered regularly in adult patients with moderate to severe pain after tonsillectomy provided rapid and effective analgesia and was well tolerated.

Alhashemi JA et al[6] compared i.v. acetaminophen with intramuscular (i.m.) meperidine with regard to analgesic effects in paediatric patients undergoing tonsillectomy. They concluded that compared with i.m. meperidine, i.v. acetaminophen provided adequate analgesia, less sedation and earlier readiness for recovery room discharge among paediatric patients undergoing tonsillectomy.

Alhashemi JA et al[7], in another study, compared i.v. acetaminophen with intramuscular (i.m.) meperidine with regard to postoperative analgesia and readiness for discharge in paediatric patients undergoing day care dental restoration. They concluded that compared with i.m. meperidine,

intraoperative i.v. acetaminophen resulted in slightly higher pain scores but earlier readiness for recovery room discharge in paediatric patients undergoing dental restoration.

Oscier et al[8] reviewed the peri-operative use of paracetamol. It reviews the pharmacology of paracetamol, highlighting new information about the mechanism of action, and examines its therapeutic use in the peri-operative period, focusing on efficacy, route of administration, and the use of a loading dose to improve early postoperative analgesia.

Sinatra RS et al[9] conducted a repeated-dose, randomized, double-blind, placebo-controlled, three-parallel group study to evaluate the analgesic efficacy and safety of intravenous acetaminophen as compared with its pro-drug Propacetamol. They concluded that intravenous acetaminophen 1g, administered over a 24-h period in patients with moderate to severe pain after orthopedic surgery provided rapid and effective analgesia and was well tolerated.

C Remy, E Marret, F Bonnet, et al[10] in their study analyzed the effect of paracetamol on morphine side-effects and consumption after major surgery and concluded that paracetamol combined with PCA induced a significant morphine sparing effect.

Ahmed Al Fadly et al[11] studied the analgesic effect of intravenous paracetamol, morphine and their combination for post operative pain after

release of post burn neck contractures and concluded that iv paracetamol effectively reduces morphine requirements by 60% or even replace it with less incidence of adverse events and more safer course during postoperative pain management after release of post burn neck contracture in adults.

Murat-et al[12] evaluated the relative analgesic efficacy of paracetamol with propacetamol for 6 hours after inguinal hernia repair under GA with ilioinguinal block in children. They concluded that a single infusion of iv paracetamol 15 mg/kg provides analgesia similar to single infusion of propacetamol 30 mg/kg following inguinal hernia repair in children.

Iolter Cattabriga et al[13] Studied the efficacy of intravenous paracetamol as an adjunctive analgesic to a tramadol-based background analgesia after cardiac surgery and concluded that in patients undergoing cardiac surgery, intravenous paracetamol in combination with tramadol provides effective pain control.

Zaka Ullah khan et al [14]conducted a prospective randomized study comparing the analgesic effect of intravenous Paracetamol with intravenous Morphine in postoperative pain control of patients undergoing knee arthroscopic surgery as day cases and concluded that both intravenous Paracetamol and intravenous Morphine seems to have the same analgesic effect. However, side effects with intravenous Paracetamol were much less.

Mehmet Turan Inal et al[15] compared the quality of analgesia and side effects of iv paracetamol versus meperidine for postoperative analgesia after elective caesarean section and concluded that i.v. paracetamol has better analgesic potency than i.v. meperidine for postoperative analgesia after caesarean section.

Duggan et al[16] reviewed all studies conducted with i.v. paracetamol and concluded that intravenous paracetamol has better analgesic effficacy in relieving pos operative pain and well tolerated.

PATHOPHYSIOLOGY OF PAIN

Introduction

Pain is a personal, subjective experience that involves sensory, emotional and behavioural factors associated with actual or potential tissue injury. What patients tell us about their pain can be very revealing, and an understanding of how the nervous system responds and adapts to pain in the short and long term is essential if we are to make sense of patients' experiences. The wide area of discomfort surrounding a wound, or even a wound that has healed long ago, such as an amputation stump, is a natural consequence of the plasticity of the nervous system. An understanding of the physiological basis of pain is helpful to the sufferer, and the professionals who have to provide appropriate treatment. It must be stated at the outset that in humans pain is invariably associated with pain behaviour and pain generally results in some degree of suffering. Nociception, neuropathy or psychological and environmental factors may singly, or in combination, result in pain.

Definition of pain

The definition of pain promulgated by the International Association for the Study of Pain is very appropriate:"Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage".

There is individual variation in response to pain, which is influenced by genetic makeup, cultural background, age and gender. Certain patient populations are at risk of inadequate pain control and require special attention. These include:

- Paediatric patients
- Geriatric patients
- Patients with difficulty in communicating (due to critical illness, cognitive impairment or language barriers)

Postoperative pain can be divided into acute pain and chronic pain:

- Acute pain is experienced immediately after surgery (up to 7 days)
- Pain which lasts more than 3 months after the injury is considered to be chronic pain

Acute and chronic pain can arise from cutaneous, deep somatic or visceral structures. Surgery is typically followed by acute pain and correct identification of the type of pain enables selection of appropriate effective treatment. The type of pain may be somatic (arising from skin, muscle, bone), visceral (arising from organs within the chest and abdomen), or neuropathic (caused by damage or dysfunction in the nervous system). Patients often experience more than one type of pain.

Positive role of pain

Acute pain plays a useful "positive" physiological role by:

- Providing a warning of tissue damage
- Inducing immobilisation to allow appropriate healing

Negative effects of pain

Short term negative effects of acute pain include:

- Emotional and physical suffering for the patient
- Sleep disturbance (with negative impact on mood and mobilisation)
- Cardiovascular side effects (such as hypertension and tachycardia)
- Increased oxygen consumption(with negative impact in the case of coronary artery disease)
- Impaired bowel movement (while opioids induce constipation or nausea, untreated pain may also be an important cause of impaired bowel movement or post operative nausea and vomitting)
- Negative effects on respiratory function (leading to atelectasis, retention of secretions and pneumonia)

Long term negative effects of acute pain:

- Severe acute pain is a risk factor for the development of chronic pain
- There is a risk of behavioural changes in children for a prolonged period (up to 1 year) after surgical pain

There are two major mechanisms in the physiology of pain:

- **Nociceptive (sensory):** Inflammatory pain due to chemical, mechanical and thermal stimuli at the nociceptors (nerves that respond to painful stimuli).
- **Neuropathic:** Pain due to neural damage in peripheral nerves or within the central nervous system.

Pain is a complex phenomenon and includes both

- Sensory – discriminative and
- Motivational – affective components

Sensory –discriminative component:

This component depends upon the ascending projection of tracts like spinothalamic and trigeminothalamic tracts into the cerebral cortex. Thus they help to perceive the quality of pain that is pricking, burning quality etc. They also help to know the location of stimulus, intensity and duration of the stimulus.

Motivational - affective component:

It includes attention, arousal, somatic, autonomic reflexes, endocrine and emotional changes. These collectively contribute to the unpleasant nature of pain.

Qualitatively there are two types of pain

1. **Fast pain -** is short, well localized, stabbing sensation that is matched to the stimulus like in pin prick, surgical incision. This pain starts abruptly when the stimulus is applied and stops when the stimulus is removed. This is due to stimulation of small myelinated Aδ fibers with conduction velocities of 12 to 30 m/s. Myelination provides junctions that permit the electrical impulses to jump which results in rapid transmission.
2. **Slow pain-** is throbbing, burning or aching sensation that is poorly localized and poorly matched to stimulus. This is due to stimulation of unmyelinated C -fibers with conduction velocity of 0.5 to 2 m/s.

Pain receptors: (Nociceptors)

These are the free nerve endings present in the skin, muscles, joints, viscera, and in the vasculature. These receptors detect the noxious stimulus due to the chemical, thermal (heat, cold) and mechanical changes. In normal tissues they are inactive and are stimulated by a sufficient energy to overcome their resting threshold. Thus they prevent random signal propagation to central nervous system for interpretation of pain. This is so called screening function. The nociceptive neurons synapse in the dorsal horn of the spinal cord with both local interneurons and projection neurons that carry the nociceptive information to the higher centres present in the brainstem, thalamus. In contrast to other sensory receptors " the pain receptors do not adapt " and this unique feature is protective and thus allows the individual be aware of continued tissue damage. After damage, pain is usually minimal and also the onset pain depends upon the rate of metabolism,

e.g. ischemic injury of the skin usually produces pain with 20 to 30 minutes, but for the exercising muscles the pain occurs within 15 to 20 seconds. Certain specific types of nociceptors react only to the specific stimuli, but other nociceptors react to multiple stimuli for e.g. “C “ nociceptors and A delta nociceptors react to heat or cold stimuli. Some Aβ receptors which are usually mechanoreceptors may have nociceptor like activity. Aβ mechanoreceptor sensory fibres can be recruited to transmit signals that interpret as painful stimuli. But it occurs only when these receptors are in the environment of inflammation. The mechanical allodynia (painful sensation results from light touch) results from Aβ receptors recruitment.

Wind-up phenomenon:

The temporal summation of number and duration of action potentials elicited per stimulus that occurs in the dorsal horn neurons has been referred to as wind-up phenomenon. This result in persistence of action potential for up to sixty seconds after stopping the stimulus and results in change in spinal cord processing that can lasts for one to three hours. Spinal cord synaptic plasticity involves binding of glutamate to NMDA receptors as well as substance P and neurokinins. Binding of glutamate to NMDA receptors alters magnesium dependent block of ion channels, which increases permeability to all cations particularly Na^+, Ca^{2+}, furthermore glutamate activates AMPA receptors which control depolarization primarily through modulation of Na^+ influx into cells. In addition to modulating augmented excitability these transmitters, cellular mechanism mediate changes in postsynaptic cells leading to permanent changes in nerve conduction. It also plays a role in the

development of central sensitisation and **intravenous paracetamol inhibits this phenomenon.**

Transmission and modulation:

Dorsal horn and its laminae act as receiving site for action potential coming from periphery via primary afferent neurons. The primary afferents terminates in the dorsal horn and synapse with secondary afferent neurons. The secondary afferent neurons act as gate cells providing initial modulation of action potentials in the dorsal horn. Two main classes of neuro-transmitters associated with primary afferent nociceptive transmission in the dorsal horn

1. Excitatory amino acids e.g., Glutamate
2. Neurokinin peptides eg., Substance P

Perception:

Thalamus and cortex:

After leaving the dorsal horn nociceptive action potentials ascends through spinothalamic tract , spinocervical tracts ,Spino reticular tracts and spino mesencephalic tracts and reach higher centers like cerebral cortex , hypothalamus reticular formation and mid brain. Afferent impulses go to reticular area and activate this area which then sends signals through thalamus and cerebral cortex. This alerts the individual to continuous tissue damage and awakens the person from sleep. These signals are poorly localized and help to alert the individual.

NMDA receptors:

NMDA receptors are postsynaptic to primary afferent neuron and located on secondary afferent neurons. They are blocked by Mg^{2+} ions. Under normal conditions, the secondary afferent neurons are not depolarized along enough to dislodge the Mg^{2+} ions from the ion channels to permit Ca^{2+} ions. Glutamate is rapidly removed from the synaptic cleft and there is no activity at NMDA receptors in normal nociceptive transmission. But in the presence of pain arising from abnormal conditions like neuropathic pain, chronic pain, peripheral sensitization, the frequency of pain signals increases which in turn increases the amount of glutamate. This glutamate depolarizes the secondary afferent neuron long enough to dislodge the Mg^{2+} which is blocking the NMDA receptors. Subsequent activation of NMDA receptors acts to activate second messengers, enzyme systems and various substances like nitric oxide that contributes to enhanced sensitivity known as central sensitization. The activation of NMDA by glutamate also activates protein kinase-C, which causes uncoupling of opioid receptors system results in decreasing responsiveness which is called opioid tolerance. Intravenous paracetamol inhibits these receptors also.

Role of sensitisation mechanisms in treatment of pain[18]

It is now recognised that a prolonged insult to the body produces changes in the nervous system which alter the "normal", "physiological" response to a noxious stimulus. As a result of the recognition of these changes, it has been proposed that pain be divided into two entities: "physiological" and "pathophysiological" or "clinical". The processes which

underlie our "physiological" experience of a noxious stimulus are quite different from the "pathophysiological" processes which occur in the clinical situation and which confront the practising clinician. Physiological pain describes the situation in which a noxious stimulus activates peripheral nociceptors, which then transmit that information through several relays, until it reaches the brain and is recognised as a potentially harmful stimulus. More commonly the insult to the body which produces pain also results in inflammation and nerve injury. The factors responsible for the development of "clinical" pain will result in a stimulus-response system that has quite different characteristics from those of "physiological" pain. **Inflammation and nerve damage give rise to changes in sensory processing at a peripheral and central level with a resultant sensitisation**. Once sensitisation has occurred, stimuli which normally would not produce pain are perceived as painful (allodynia) and there is an exaggerated response to painful stimuli (hyperalgesia). In particular, surgery produces a biphasic insult on the human body which has implications for pain management. Firstly, during surgery there is trauma to tissue, which produces a barrage of nociceptive input. Secondly, after surgery there is an inflammatory response at the site of injury which is also responsible for the generation of noxious input. Both of these processes, which occur during and after surgery, result in sensitisation of pain pathways. This occurs at a peripheral level where there is a reduction in the threshold of nociceptor afferents and at a central level with an increase in excitability of spinal neurons involved in pain transmission. This sensitisation has now been characterised. It has profound implications for the management of acute pain and has provoked interest in the use of pre-emptive analgesia

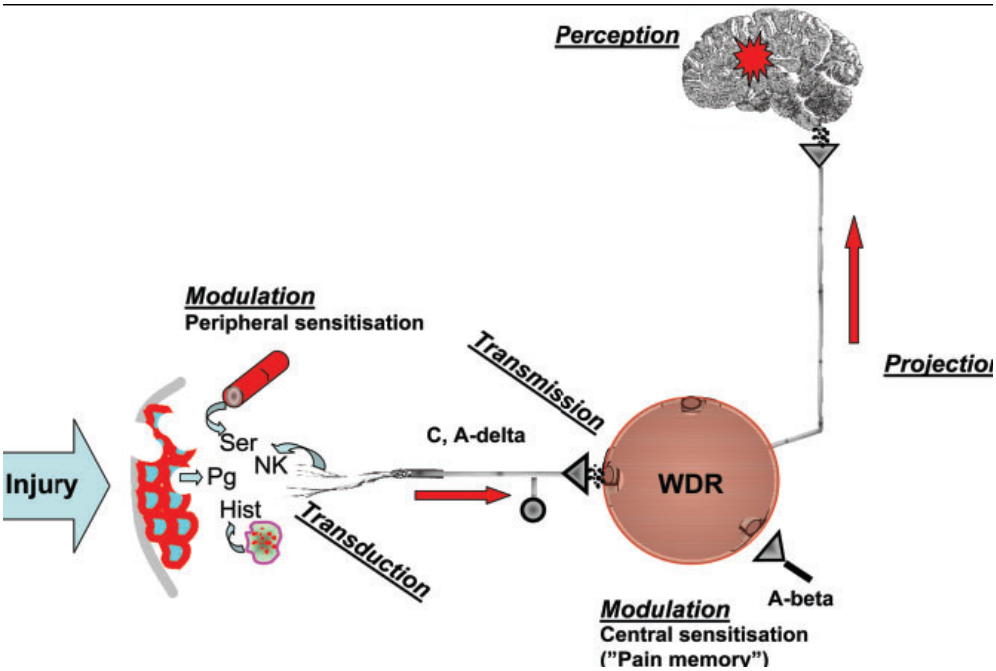
and new methods of postoperative pain management with new agents of non-opioid type, possibly combined with opioid drugs.

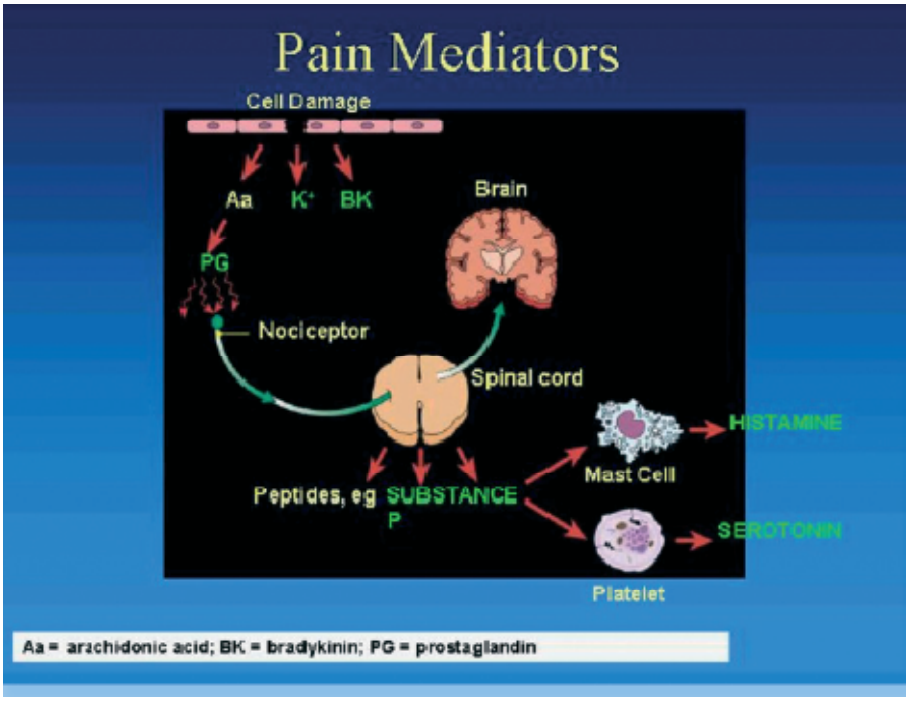
Central sensitization [17,18,19]

The responses in the CNS are primarily physiological. Following injury, there is also an increased responsiveness to normally innocuous mechanical stimuli (allodynia) and a zone of secondary hyperalgesia in uninjured tissue surrounding the site of injury. These changes are believed to be a result of processes that occur in the dorsal horn of the spinal cord following injury. This is the phenomenon of central sensitisation. These changes indicate that, in the presence of pain, the central nervous system is not "hard-wired" but plastic, and the attempts to modify pain must take into account these changes. A barrage of nociceptive input, such as which occur with surgery, results in changes to the response properties of dorsal horn neurons. It has been demonstrated that a painful stimulus, which is at a level sufficient to activate C fibres, does not only activate dorsal horn neurons. It can also be observed that neuronal activity progressively increases throughout the duration of the stimulus. Therefore, with nociceptive input there is not a simple stimulus-response relationship but a "wind-up" of spinal cord neuron activity. This "wind-up" may make these neurons more sensitive to other input and is a component of central sensitisation. This finding has had a profound influence on concepts of pain and it is now known that a sustained C-fibre barrage in primary afferent fibres leads to other morphological and biochemical changes in the dorsal horn which may be difficult to reverse. Several other changes have been noted to occur in the dorsal horn with central sensitisation. Firstly,

there is an expansion in receptive field size so that a spinal neuron will respond to stimuli that would normally be outside the region which responds to nociceptive stimuli. Secondly, there is an increase in the magnitude and duration of the response to stimuli which are above threshold in strength. Lastly there is a reduction in threshold so that stimuli which are not normally noxious activate neurons which usually transmit nociceptive information. These changes may be important both in acute pain states, such as postoperative pain, and in the development of chronic pain. They manifest by the presence of hyperalgesia, allodynia and an increase in the size of the area of tenderness around a wound or injury. Nerve injury also results in changes in the dorsal horn. It has been demonstrated that following peripheral nerve injury the terminals of myelinated afferents sprout in neighbouring regions of the dorsal horn. This means that nerves which do not usually transmit pain sprout into a more superficial region of the dorsal horn that normally acts as a relay in pain transmission. If functional contact is made between these terminals which normally transmit non-noxious information and neurons that normally receive nociceptive input, this may provide a framework for the pain and hypersensitivity to light touch that is seen following nerve injury.

Central sentisation[20]





Peripheral sensitisation

Several different types of stimuli can result in activation of the peripheral nociceptive pathway which ultimately results in the perception of pain. Under normal conditions, thermal, mechanical and chemical stimuli activate high threshold nociceptors which signal this information to the first relay in the dorsal horn. However, under clinical conditions application of a noxious stimulus is usually prolonged and traumatic and associated with tissue damage. Tissue damage results in an inflammatory response which directly affects pain sensation. Part of the inflammatory response is release of intracellular contents from damaged cells and inflammatory cells such as mast cells, macrophages and lymphocytes. Nociceptive stimulation also results in a neurogenic inflammatory response. This produces vasodilatation and extravasation of plasma proteins, as well as action on inflammatory cells to release chemical mediators. These interactions result in the release of a "soup" of inflammatory mediators such as potassium, serotonin, bradykinin, substance P, histamine and products from the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism. These chemicals then act to sensitise high threshold nociceptors. Following sensitisation, low intensity stimuli which would not normally cause pain are now perceived as painful. This series of events which follows tissue injury is termed **peripheral sensitisation**. It is characterised by an increased responsiveness to thermal stimuli at the site of injury. If attempts are to be made to reduce the phenomenon of peripheral sensitisation, then efforts need to be focused on preventing or reducing the action of chemical mediators in the inflammatory "soup". This is the rationale for the current use of nonsteroidal anti-

inflammatory drugs (NSAIDs) and in the future for use of other peripherally administered drugs such as conventional opioids, "peripherally acting" opioids, local anaesthetics (conventional and long acting) and so on. Inflammation also appears to have another important effect on peripheral nerves. It has been found that there is a class of unmyelinated primary afferent fibres that do not normally respond to excessive mechanical or thermal stimuli. However, in the presence of inflammation and chemical sensitisation they then become responsive and discharge vigorously even during ordinary movement. They also display changes in receptive fields. The properties of these receptors still require characterisation, but they have been identified in a number of different tissues and species and are termed "silent" nociceptors.

PRE-EMPTIVE ANALGESIA

Preemptive analgesia[20,21,22] is an attractive concept of addressing pain even before it starts. The concept was propounded in the early 1980s when experimental studies showed that measures to antagonize the nociceptive signals before injury prevented central hypersensitisation, thereby reducing the intensity of pain following the injury. Transmission of pain signals evoked by tissue damage leads to sensitization of the peripheral and central pain pathways. Pre-emptive analgesia is a treatment that is initiated before the surgical procedure in order to reduce this sensitization. Owing to this 'protective' effect on the nociceptive system, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Theoretically, immediate postoperative pain may be reduced and the development of chronic pain may be prevented. Although some clinical studies have demonstrated significant effects on acute postoperative pain, no major clinical benefits of pre-emptive analgesia have been documented. The only way to prevent sensitization of the nociceptive system might be to block completely any pain signal originating from the surgical wound from the time of incision until final wound healing. It refers to the administration of an analgesic before a painful stimulus, such as tissue injury during surgery, in an attempt to obtain better pain relief compared with when the same analgesic intervention is used after the painful stimulus. Preemptive analgesia is known to prevent central sensitization of pain, thereby reducing hyperalgesia. There

is also the “wind-up” phenomenon which causes persistent spontaneous pain even in the absence of peripheral stimuli.

Preemptive analgesia is defined as an anti-nociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain. By decreasing the altered central sensory processing, preemptive analgesia is thought to consequently decrease the incidence of hyperalgesia and allodynia after surgery. The definition of preemptive analgesia has varied, thereby causing confusion and misunderstanding of the concept. It is important to consider this definition in clinical trials for determining the effectiveness of preemptive analgesia. The emphasis of preemptive analgesia is on the pathophysiologic phenomenon that it should prevent altered sensory processing. Therefore, preemptive may not simply mean “before incision.” An insufficient afferent blockade cannot be preemptive, even if it is administered before the incision.

Hence, the primary goals of preemptive analgesia are

1. To decrease acute pain following tissue injury
2. To prevent pathological modulation of the central nervous system (CNS) due to this pain and
3. To prevent development of chronic pain.

In the present study, i.v paracetamol was used as a preemptive analgesic in relieving post operative pain.

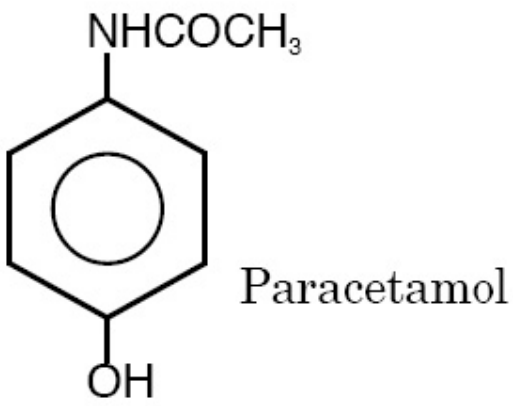
PHARMACOLOGY OF PARACETAMOL

History:

In 1877, Harmon Northrop Morse synthesized Para-acetyl-amino-phenol at John Hopkins University. But it wasn't until 1887 that Joseph Von Merring tried Paracetamol on patients. Paracetamol was first used in medicine by Von Mering in 1893. It gained popularity only after 1949. Paracetamol was marketed in USA in 1953 and introduced as a 500mg tablet in the UK in 1956.

Structure of Paracetamol

Para-acetyl-amino-phenol



Composition of IV Paracetamol

1) Cysteine Hydro Chloride Mono hydrate.
2) Di Sodium Phosphate di hydrate.
3) Hydro chloric acid.
4) Mannitol.
5) Sodium hydroxide.
6) Water for injection.

Mechanism of action[8]

The mechanism of action remains unclear as , unlike opioids and NSAIDs, paracetamol has no known endogenous binding sites and does not inhibit peripheral cyclooxygenase activity significantly. There is increasing evidence of a central antinociceptive effect, and potential mechanisms for this include inhibition of a central nervous system COX-2, inhibition of a putative central cyclooxygenase 'COX-3' that is selectively susceptible to paracetamol, and modulation of inhibitory descending serotinergic pathways. Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclooxygenase activity. Paracetamol is therefore an effective postoperative analgesic, with potency slightly less than a standard dose of morphine or the NSAIDs. The introduction of an i.v. preparation and reports of the analgesic and anti-inflammatory properties and safety advantages of a nitric oxide (NO) releasing form may represent significant advances in the use of this drug. Paracetamol acts on both the peripheral and central component of pain pathway. Paracetamol inhibits both isoforms of cyclo-oxygenase (COX); the constitutive COX 1, and the inducible COX-2. Non-steroidal anti-inflammatory drugs (NSAIDs) also act by inhibition of COX, yet important differences exist; notably, paracetamol displays weak anti-inflammatory activity, few or no gastrointestinal, and only a small dose-dependent alteration of platelet function. Recent studies show that it is a cox-3 inhibitor[23,24] which is a splice variant of cox-1 which selectively inhibits the nervous system prostaglandin synthesis. Other central mechanisms of action depend on the bulbo-spinal serotoninergic pathway[25,26]. It is also an indirect

activator of cannabinoid CB1 receptors. By direct inhibition of the NMDA receptor it inhibits the substance P dependent synthesis of nitric oxide which is a primary mediator of nociception. Paracetamol has analgesic and antipyretic effects similar to those of aspirin. It has only weak anti inflammatory affects. It has a poor ability to inhibit cyclooxygenase (**COX)** in the presence of high concentration of peroxides as are found at the sites of inflammation. **COX** might be disproportionately pronounced in the brain explaining the antipyretic activity of paracetamol.

Pharmacodynamics[27]:

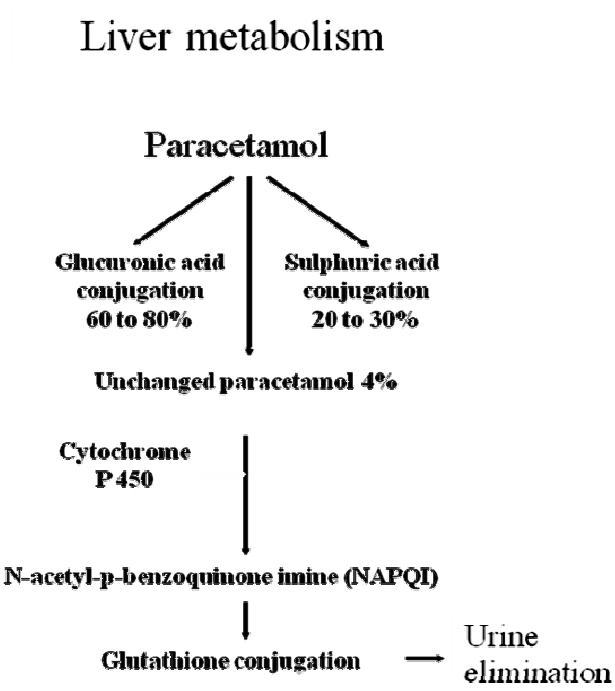
Intravenous Paracetamol is very well tolerated. Hypersensitivity reactions are rare. Onset of analgesia occurs rapidly within 5-10 mins of IV administration. Peak analgesic effect occurs in 1 hour with a mean duration of 4-6 hours. The antipyretic effect of IV pracetamol is also rapid with fever reduction within 30 minutes of administration and lasting for at least 6 hours. Single or repeated therapeutic doses have no effect on the cardio-vascular and respiratory systems, on platelets or on coagulation. Acid base changes, uricosuric effects do not occur. The drug does not produce gastric irritation, erosion, or bleeding as with salicylates.

Pharmacokinetics [27,28]

Paracetamol displays linear pharmacokinetics at dosages of 4-8/ gm per day. Following single dose of paracetamol 1gm, the mean maximum plasma concentration (Cmax) was 29.9 µg/ml at the end of 15-min infusion period. C_{max} was approximately two fold higher after IV paracetamol than after oral paracetamol. Mean volume of distribution for IV Paracetamol 1g was 85 L**.** It rapidly penetrates into CSF and does not extensively bind to plasma proteins. It is not subjected to significant first pass metabolism. Oral bioavailability is estimated between 63 – 89%. Therapeutic level for action is only a plasma concentration of 10 – 20 µ/ml whereas the threshold for potential hepatotoxicity is 150 µ/ml. Hence there is a wide margin of safety between therapeutic dose and toxicity.

Metabolism [29,30,31]

Metabolized in the liver by glucuronidation and sulfation. At higher doses it is metabolized by the cytochrome p450 enzyme pathway to produce the reactive intermediate **N-acetyl-p-benzo-quinone imine** (NAPQI). Toxic effects are due to this metabolite. NAPQI is eliminated by the liver by a reaction with tripeptide glutathione. If not eliminated, NAPQI begins to react with cellular proteins & nucleic acids causing irreparable damage.



At therapeutic doses, only a small fraction (<4%) is metabolized by cytochrome P450 to a reactive intermediate N-acetyl-p-benzoquinone imine (NAPQI) which is responsible for toxicity in many organs, including the liver. Although the major concern with paracetamol administration relates to the potential for hepatotoxicity, this is extremely rare following therapeutic dosing[31]. In patients with severe disease[32,33,34,35], however, the elimination half-life can be prolonged. Alcohol induces CYP2E1, the main enzyme catalysing NAPQI formation, but inhibits its activity while it remains in the body. Under normal conditions, NAPQI is rapidly detoxified by reduced glutathione and eliminated in the urine. Therefore co-administration of alcohol with paracetamol may initially be protective, but once alcohol is cleared from the body, the risk of hepatotoxicity from overdose is increased [36,37,38]. In adults, hepatotoxicity may occur after a single dose of 10 to 15g (150 to

250mg/kg) of paracetamol because the glutathione stores are exhausted by the generation of large amounts of NAPQI.Therapeutic dosing may elevate serum alanine aminotransferase (ALT) in healthy adults who consume alcohol in moderation or not at all, but isolated elevations in aminotransferases are unlikely to be of clinical significance.[39,40,41] Paracetamol has recently been shown to have a dose dependent anti-aggregatory effect on platelets, mediated through inhibition of platelet COX-1 and subsequent decreased synthesis of thromboxane A_2[42]. Inhibition is observed after a standard dose of 15 mg.kg, but the degree of inhibition is significantly less than is seen with NSAIDs such as diclofenac [43], and surgical bleeding attributable to paracetamol is unlikely.

Elimination

Metabolites are excreted in the urine as glucuronide (60-80%) and sulfide (20-30%) conjugates with less than 5% of the drug excreted unchanged. Less than 1% is recovered in bile. Elimination half life of Paracetamol 1g is 2.7 hours and its rate of systemic clearance is 17.9 litres per hour.

In Paediatrics [44,45]:

1) Neonates and children upto 10 yrs of age excrete less glucuronide conjugates and more sulfate conjugates than adults.
2) Elimination half life is shorter in children (1.5 – 2 hrs than adults) and longer in neonates (3.5 hrs)

3) Pharmacokinetics is similar to that of adults with the exception of t1/2 ß

4) $t_{1/2}$ß is shorter in children (1.5-2.0 hrs) than adults, lower in neonates,(3.5 hours) than adults. Systemic clearance rate of IV Paracetamol (10, 12.5 or 15 mg/kg) for neonates aged 28-32 weeks, 32-36 week and >36 week was estimated to be 5.24 L/h/70 kg, with a Volume of distribution of 76L/70 kg. Clearance rate increases with gestational age.

Elderly

Pharmacokinetics is not changed in elderly subjects.

MATERIALS AND METHODS

Study design:

Prospective, randomized, double blinded, comparative study.

Double blinding was done by taking appropriate dose of intravenous paracetamol calculated in mg/kg and was added to a solution of normal saline to make a volume of 100 ml. This was labelled as drug A. Plain 100 ml of normal saline was labelled as drug B. Neither the person administering the drug nor the person observing the patient in the post operative period did not know the drug.

Study population:

After obtaining the institutional ethical committee approval and written informed consent from the parent/guardian, 70 ASA I physical status patients undergoing tonsillectomy were selected between the age group of 6-16 years and weighing between 10-30 kg.

Sample size:

35 patients in the paracetamol group (P group) and 35 in the control group (N group).

Probability sampling: All the70 patients were randomised in two groups and the entire patients stood an equal chance of getting into any group.

Data collection:

- Age, Sex, Weight
- Pre operative and intra operative pulse rate and blood pressure, Spo2
- Duration of surgery
- Sedation score using Ramsays Sedation Scale
- Visual analogue pain scale at the end of surgery, 1h 2h,3h,4h,5h,6h.
- Post operative complications such as
    - Drug intolerance
    - Nausea and vomiting
    - Epigastric pain
    - Bleeding

Exclusion criteria

- Upper and lower respiratory tract infections
- Cardiac valvular abnormalities
- Abnormal bleeding and clotting time
- Obstructive sleep apnea
- Known history of allergy to paracetamol
- Past history of jaundice
- Patients on aspirin
- Any other concurrent antipyretic, analgesic or anti inflammatory medications

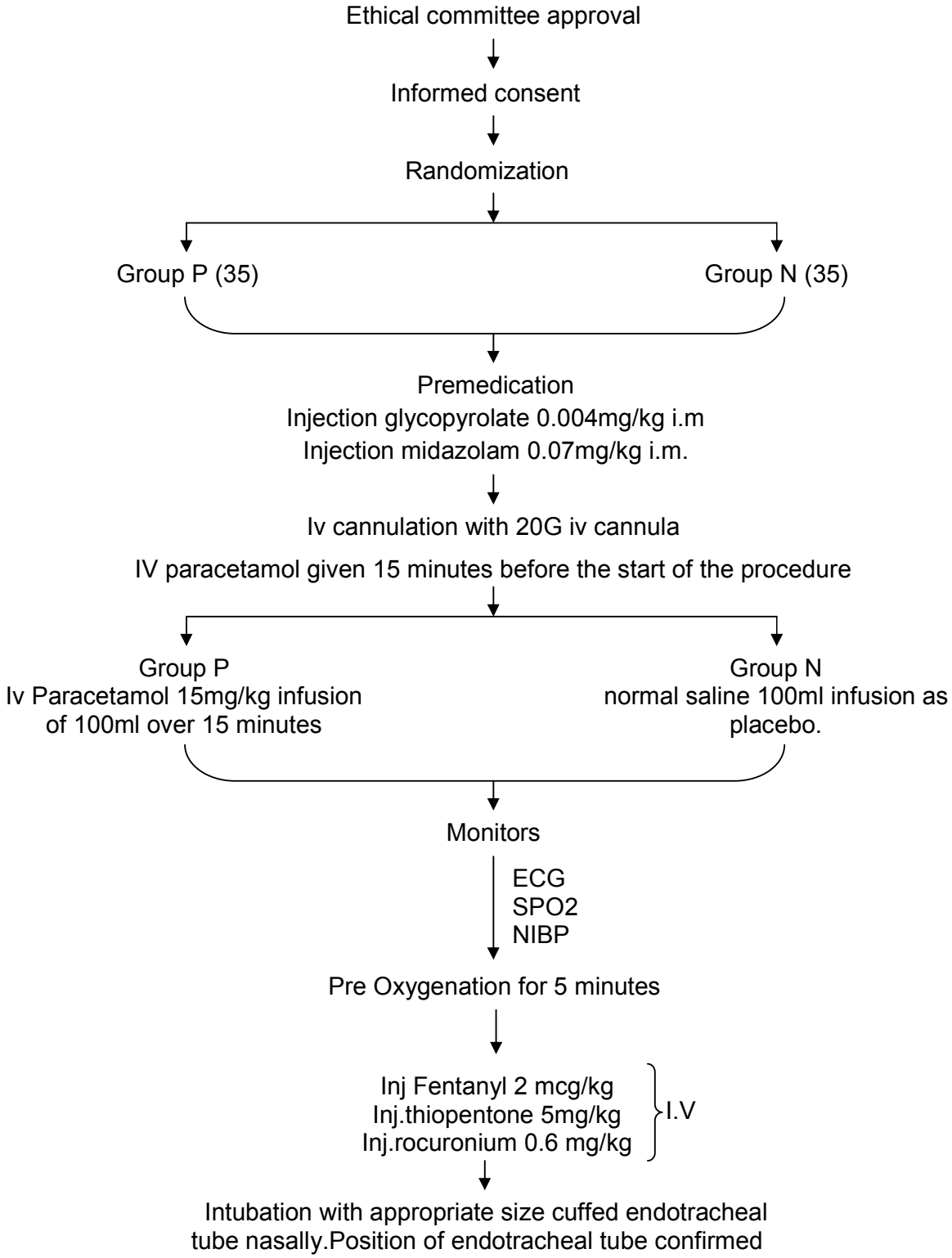
PRE OPERATIVE EVALUATION:-

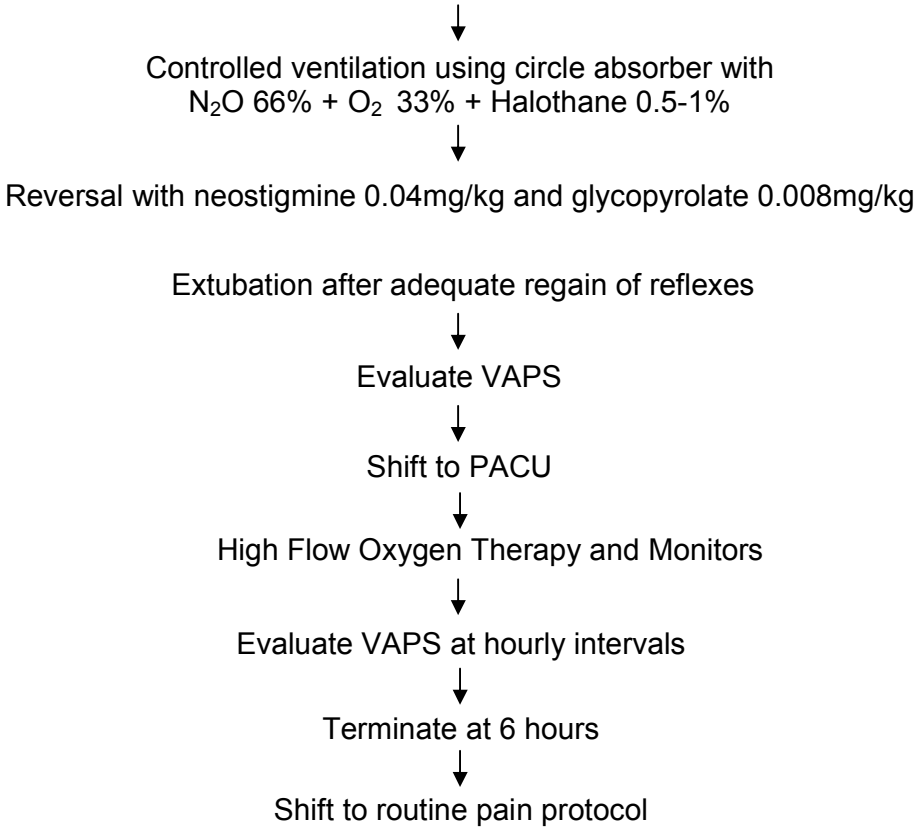
History regarding previous anaesthesia, surgery, any significant medical illness, medications and allergy were recorded. Age, Inpatient Number, Body Weight, Baseline vital parameters were recorded. Complete physical examination and airway assessment were done.

Following laboratory investigations were done:

- Blood grouping and typing
- Complete Hemogram
- Coagulation profile
- Blood: sugar, urea
- Serum Creatinine
- Serum Electrolytes: Na+, K+
- ECG in all leads

ANAESTHESIA PROTOCOL:





Post-operatively the patients were monitored for changes in pulse rate, MAP, Spo2 for a period of 6 hours and were instructed to mark a point on the 10 point visual analog pain scale according to the intensity of pain. The pain relief was graded as follows in VAPS.

VISUAL ANALOG PAIN SCALE

Pain Score	Quality of analgesia
0 -1	Excellent
2 – 4	Good
5 – 6	Fair
7 – 8	Poor
9 – 10	No relief

The pain score was assessed for a period of 6 hours and the total duration of post operative analgesia was taken as the period from the end of surgery till the first requirement of systemic analgesic medication.

In both the groups patients were given the first analgesic medication when the VAPS score was 4 and above. Patients were observed for any side effects like intolerance, bleeding, epigastric pain, PONV.

Sedation score was assessed using **Ramsays sedation scale**[52] as follows.

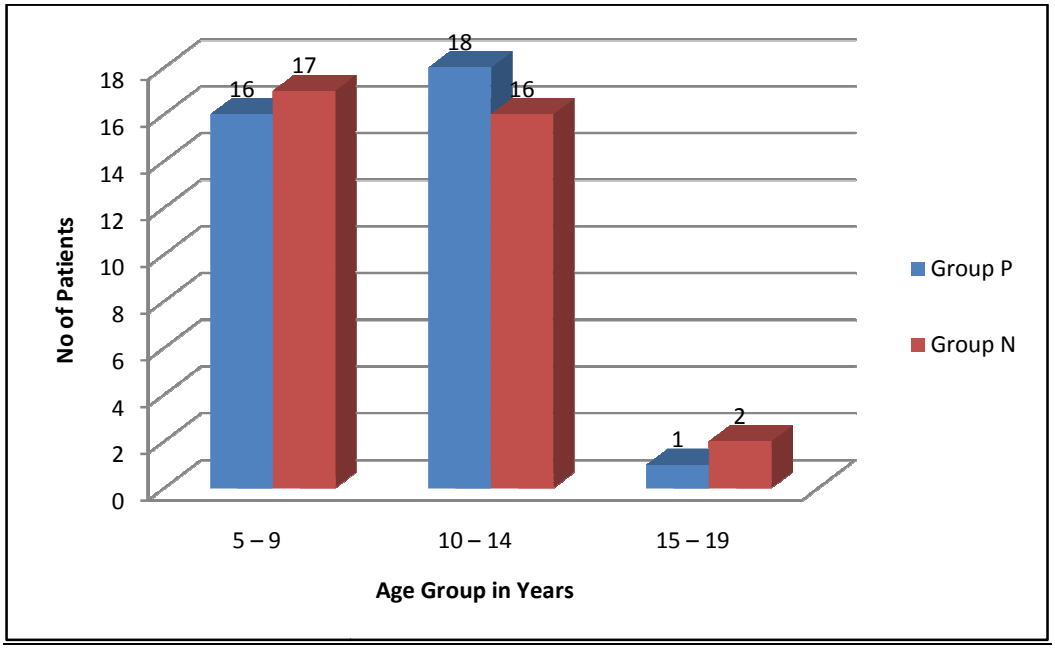
1. Anxious and agitated or restless, or both
2. Co-operative, oriented, and calm
3. Responsive to commands only
4. Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5. Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6. Unresponsive

OBSERVATION AND RESULTS

Data were analysed using SPSS version 13.0 computer software at level of significance p = 0.05. Numerical variables were presented as mean and standard deviation (SD) and categorical variables were presented as frequency (%). Unpaired Student ‘t’ test was used for between-group comparisons between categorical variables. Time to first analgesic administration was analysed by the Kaplan–Meier survival analysis.

COMPARISON OF THE TWO GROUPS BY THEIR AGE

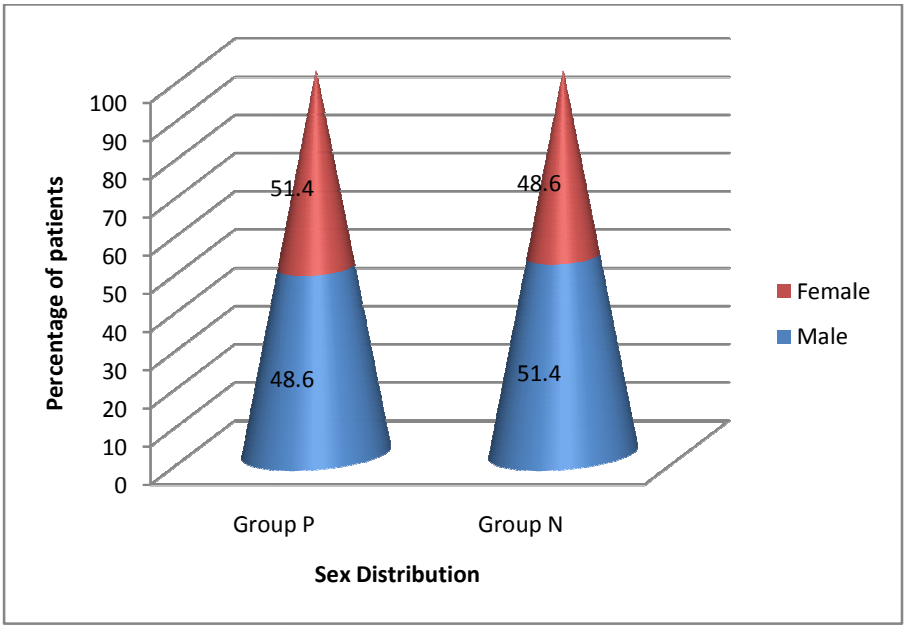
AGE GROUP YRS	Group P PARACETAMOL		Group N PLACEBO		Total	
	No	%	No	%	No	%
5 – 9	16	45.7	17	48.6	33	47.1
10 – 14	18	51.4	16	45.7	34	48.6
15 – 19	1	2.9	2	5.7	3	4.3
TOTAL	35	100	35	100	70	100
MEAN ±SD	9.7 ± 1.9		9.8 ± 2.8		9.8 ± 2.7	
Significance	P = 0.898 Not significant					



The mean ages between the two groups were 9.7 ± 1.9 and 9.8 ± 2.8 for P and N group respectively. The difference between two mean ages was not statistically significant (P>0.05).

SEX DISTRIBUTION

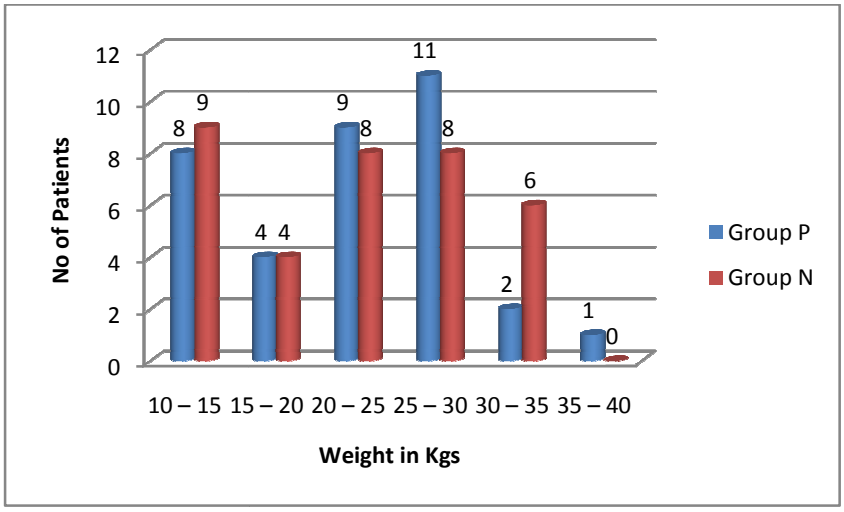
SEX	Group P		Group N		't' value	Significance
	No	%	No	%		
Male	17	48.6	18	51.4	0.273	P>0.05
Female	18	51.4	17	48.6		
Total	35	100	35	100		



The ratio of male to female remained the same in both P and N groups. The difference in percentage between two groups was not statistically significant.

Matching of the P and N group with reference to their body weight

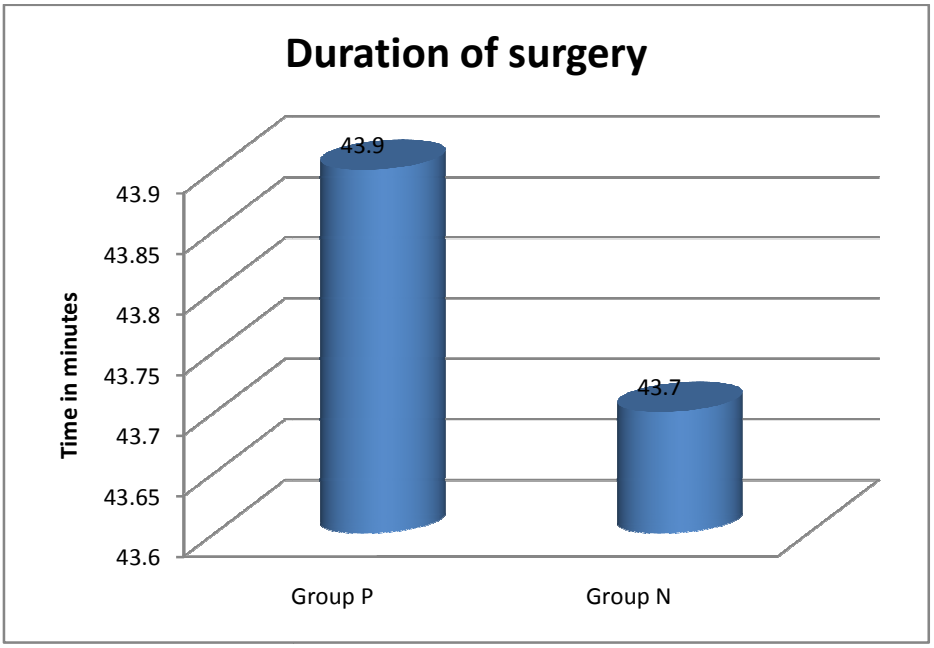
WEIGHT Kgs	Group P PARACETAMOL		Group N	
	No	%	No	%
10 – 15	8	22.9	9	25.7
15 – 20	4	11.4	4	11.4
20 – 25	9	25.7	8	22.9
25 – 30	11	31.4	8	22.9
30 – 35	2	5.7	6	17.1
35 – 40	1	2.0	0	0
TOTAL	35	100	35	100
MEAN ± SD	20.4 ± 6.3		20.3 ± 6.7	
't'	0.036			
Significance	P = 0.971 NS			



The mean weights between the two groups were 61.1 ± 3.2 and 59.7 ± 3.5 for P and N group respectively. The difference between two mean weights was not statistically significant (P > 0.05).

Duration of surgery

Measured variables	Group P		Group N		't'	Significance
	Mean	S.D	mean	S.D		
Duration of surgery (min)	43.9	5.7	43.7	5.7	0.105	P > 0.05 NS

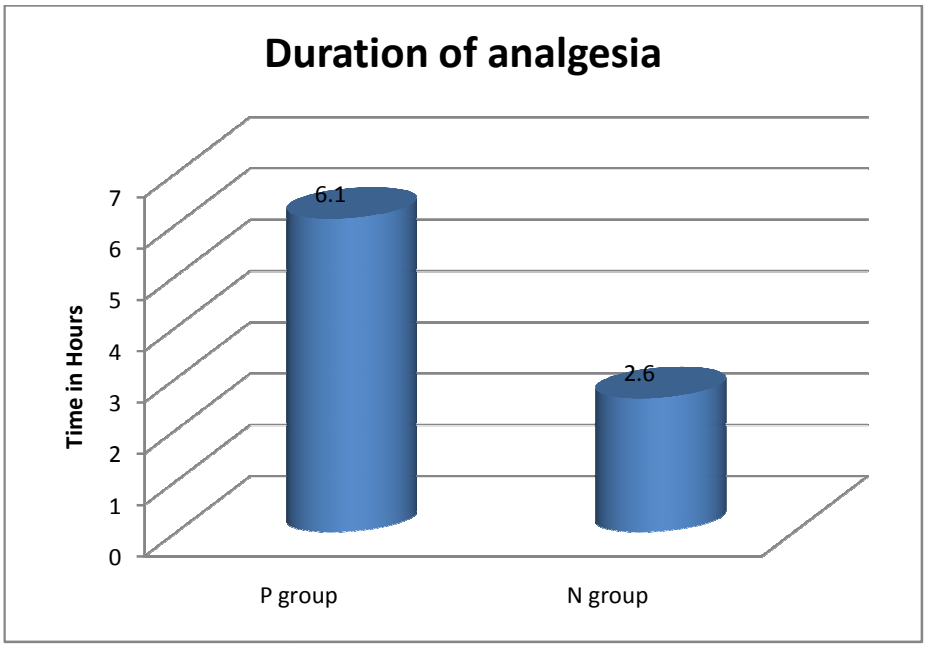


The duration of surgery for both groups was comparable and was found statistically not significant.

The two groups were compared with reference to their age, sex, weight and duration of surgery and they were amenable for comparison of other variables like duration of analgesia and haemodynamic variables such as MAP, PR and SpO_2.

Comparison of duration of analgesia

Variable	P group		N group		Mean Difference	't'	Diff	significance
	Mean	SD	Mean	SD				
Duration of analgesia (hrs)	6.1	0.5	2.6	0.3	3.5	33.608	68	P < 0.001

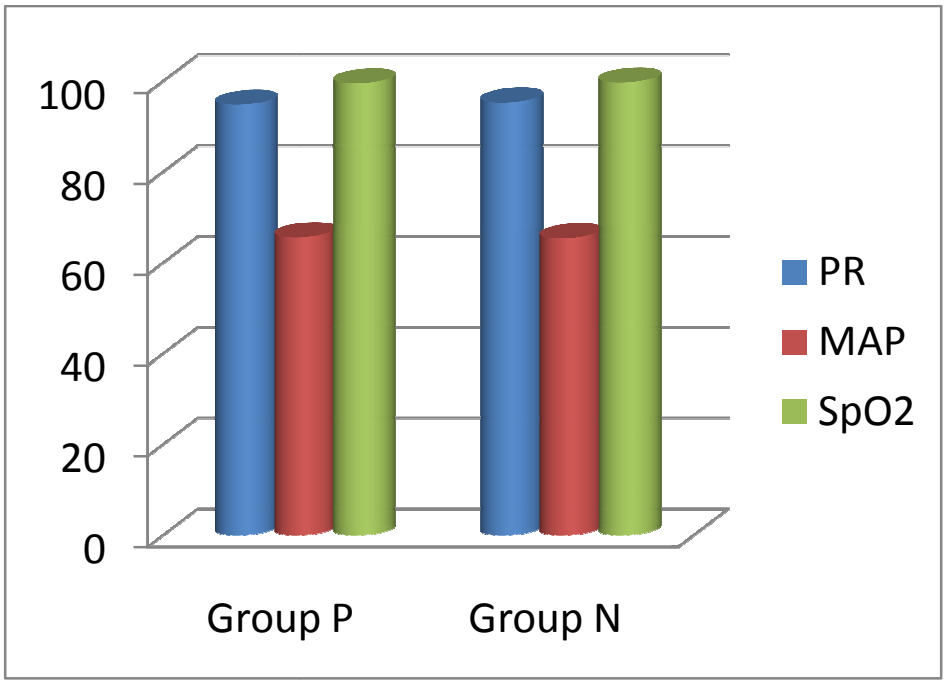


Stastistically significant (p<0.001) prolongation of duration of analgesia in the paracetamol group lasting for about 6.1 hours in the postoperative period as compared to placebo group which was only 2.6 hours.

Comparison of hemodynamic variables between the two groups

Hemodynamic variables in the pre operative period

Measured variables	Group P		Group N		't'	Significance
	Mean	S.D	mean	S.D		
Pulse rate	94.8	6.1	95.3	6.0	0.376	P = 0.376 NS
MAP	65.6	0.6	65.4	0.8	1.030	P =0.307 NS
SpO_2	99.5	0.5	99.7	0.5	1.695	P = 0.095 NS

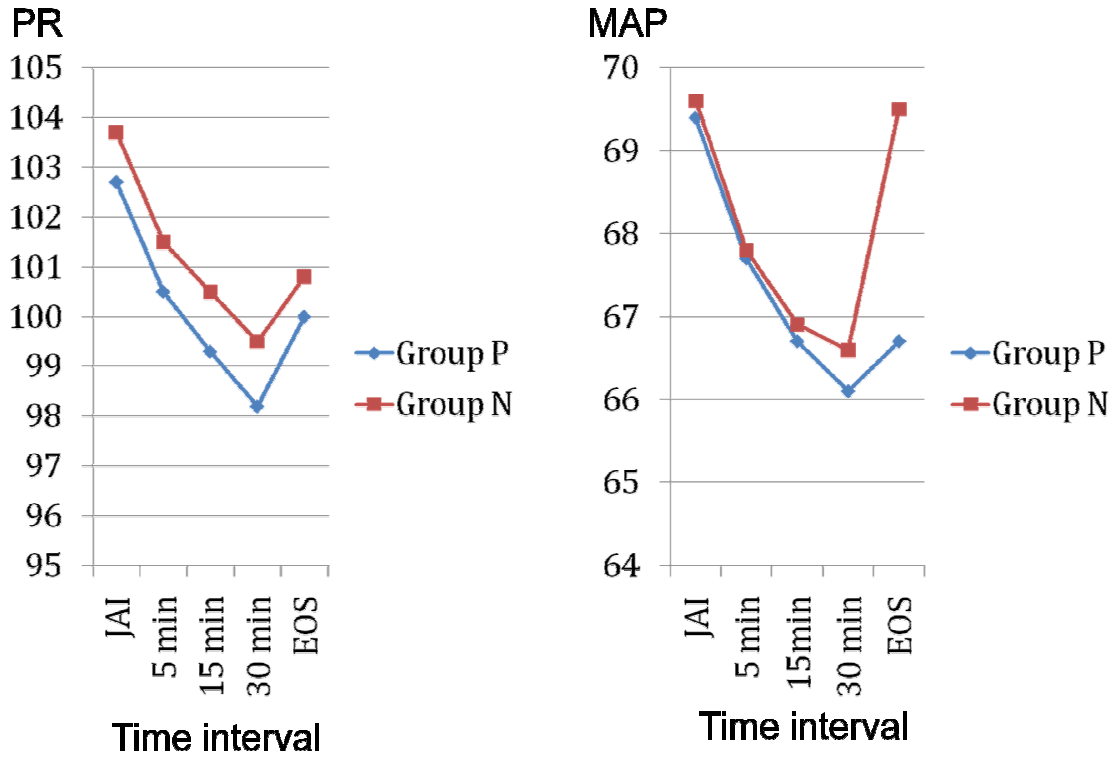


The pulse rate, MAP and SpO_2 of both groups reveals that there was no statistically significant difference between both the groups before surgery ($p>0.05$)

Hemodynamic variables in the intra operative period

Time interval	variables	Group P		Group N		't'	Significance
		Mean	SD	mean	SD		
Just after induction	PR	102.7	4.5	103.7	5.2	0.886	P = 0.379
	MAP	69.4	0.6	69.6	0.8	1.030	P = 0.307
	SpO_2	99.5	0.5	99.5	0.5	0	P = 1
5 min	PR	100.5	4.3	103.7	5.2	0.886	P = 0.379
	MAP	67.7	0.7	67.8	1.1	0.663	P = 0.510
	SpO2	99.7	0.5	99.7	0.5	0	P = 1
15min	PR	99.3	4.3	100.5	5.0	1.076	P = 0.286
	MAP	66.7	0.8	66.9	0.9	1.247	P = 1.247
	SpO2	99.5	0.5	99.5	0.5	0	P = 1
30 min	PR	98.2	4.2	99.5	5.1	1.154	P = 0.254
	MAP	66.1	1.2	66.6	1.2	1.902	P = 0.061
	SpO2	99.5	0.5	99.5	0.5	0	P = 1
End of surgery	PR	100.0	4.0	100.8	4.7	0.709	P = 0.481
	MAP	66.7	1.6	69.5	0.7	9.5	P = 0.061
	SpO2	99.5	0.5	99.5	0.5	0	P = 1

Hemodynamic variables in the intra operative period

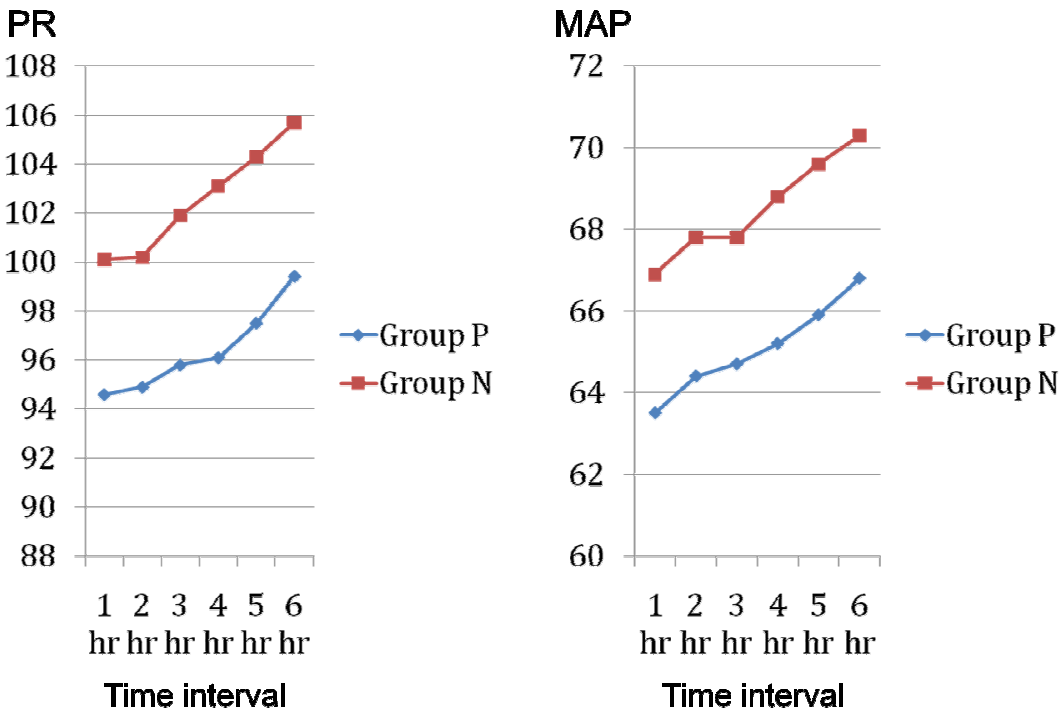


The pulse rate, MAP and SpO_2 of both groups reveals that there was no statistically significant difference between both the groups during surgery ($p>0.05$)

Post operative haemodynamic variables

Time interval	variables	Group P		Group N		' t '	Significance
		Mean	SD	Mean	SD		
1 hr	PR	94.6	3.3	100.1	4.7	5.701	P = 0.000
	MAP	63.5	0.9	66.9	1.3	12.540	P = 0.000
	SpO2	99.7	0.5	99.5	0.5	1.450	P = 0.152
2 hr	PR	94.9	2.7	100.2	4.5	5.905	P = 0
	MAP	64.4	1.2	67.8	1.2	11.724	P = 0
	SpO2	99.7	0.5	99.5	0.5	1.450	P = 0.152
3 hr	PR	95.8	2.7	101.9	4.4	6.945	P = 0
	MAP	64.7	1.1	67.8	1.2	11.159	P = 0
	SpO2	99.5	0.5	99.7	0.5	1.209	0.231
4 hr	PR	96.1	2.9	103.1	4.6	7.672	P = 0
	MAP	65.2	1.1	68.8	1.2	13.454	P = 0
	SpO2	99.5	0.5	99.5	0.5	0.236	P = 0.814
5 hr	PR	97.5	2.5	104.3	4.4	7.942	P = 0
	MAP	65.9	1.3	69.6	1.3	12.163	P = 0
	SpO2	99.5	0.5	99.5	0.5	0	P = 1
6 hr	PR	99.4	2.6	105.7	4.1	7.572	P = 0
	MAP	66.8	1.1	70.3	1.1	12.781	P = 0
	SpO2	99.7	0.5	99.5	0.5	1.450	P = 0.152

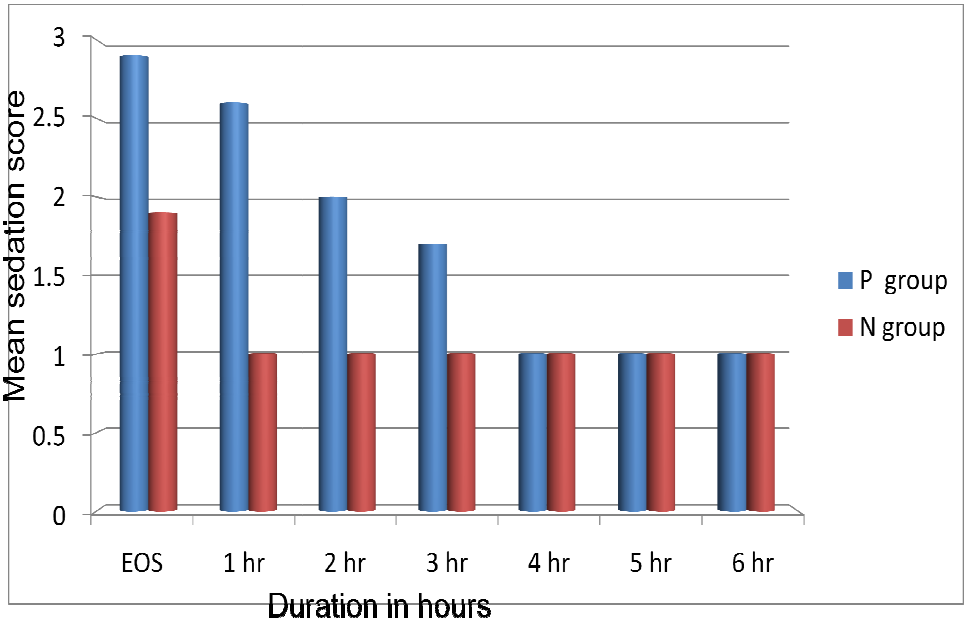
Post operative haemodynamic variables



As shown in the table above, the mean pulse rate at 0 – 6 hours in the post operative period for P group was significantly lower than the N group with $P < 0.001$. The mean MAP at 0 – 6 hrs in the post operative period was significantly higher in N group than P group with $P < 0.001$. There was no significant difference in respect to mean post operative SpO2 in both groups.

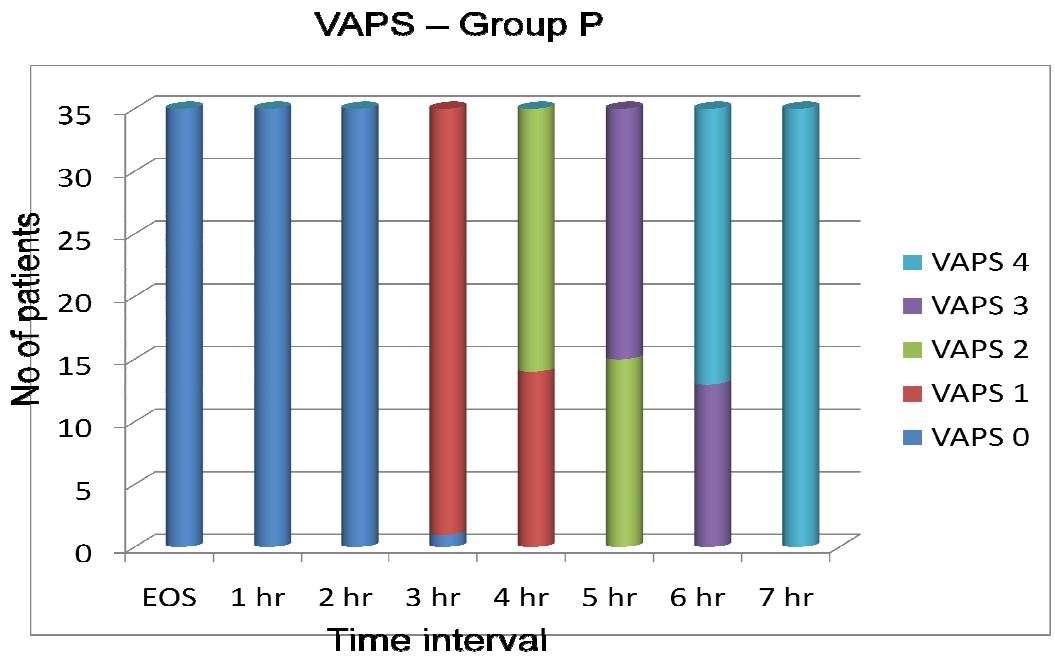
Post operative Sedation score

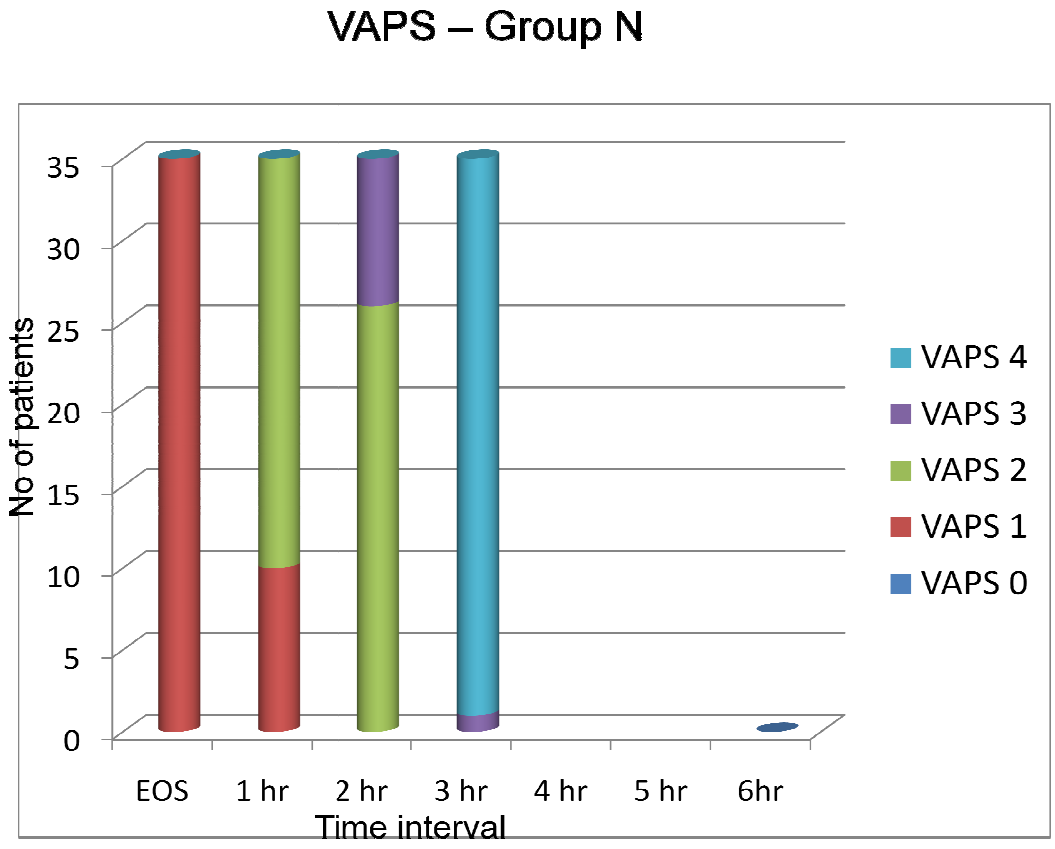
Time interval	Group P		Group N		' t '	Significance
	Mean	SD	Mean	SD		
EOS	2.9	0.3	1.9	0.2	15.576	P < 0.001
1 hr	2.6	0.5	1.0	0	19.653	P < 0.001
2 hr	2.0	0.0	1.0	0.0	0	0
3 hr	1.7	0.4	1.0	0.0	9.911	P < 0.001
4 hr	1.0	0.0	1.0	0.0	0	0
5 hr	1.0	0.0	1.0	0.0	0	0
6 hr	1.0	0.0	1.0	0.0	0	0



Statistically significant conscious sedation was observed in paracetamol group with a score of 2.6 at the end of first hour, 2 at the end of second hour, 1.7 at the end of 3 hours after that both the groups were with a mean score of 1 up to six hours in post operative period.

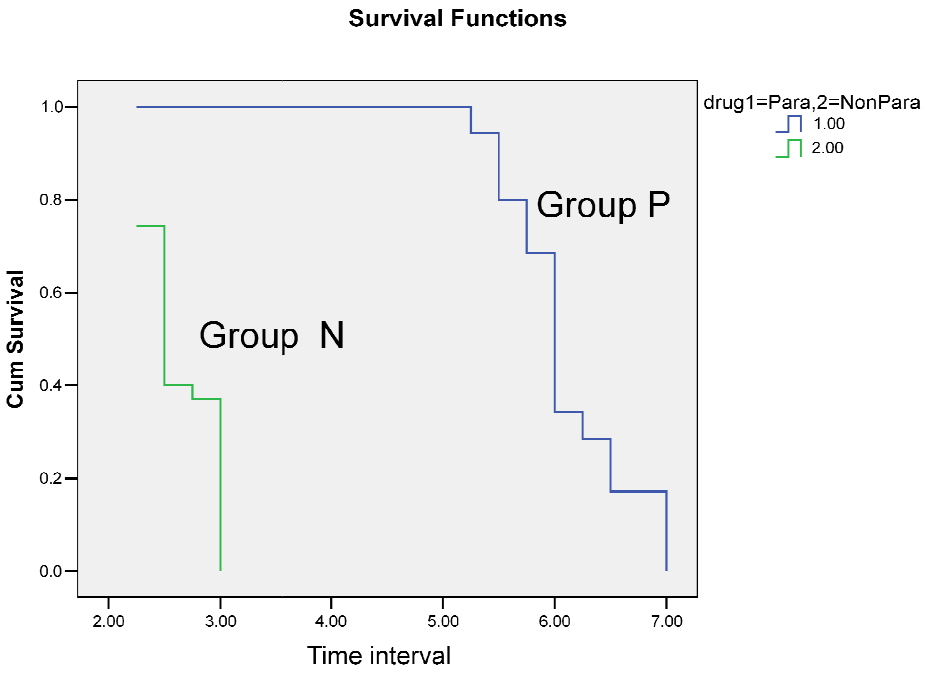
Post operative pain assessment using visual analog pain scale





This graph compares the quality of analgesia assessed by using VAPS score between 0-10 with 0 being excellent pain relief and score of 10 being the worst pain ever. Patients in both the groups were given rescue analgesic in the form of intramuscular diclofenac 1.5mg/kg if the VAPS score was more than 4. In the P group all patients had a VAPS score of 4 after a mean duration of 6 hours while in the N group a VAPS score of 4 was attained even before the end of 2.5 hours and rescue analgesic was given.

Kaplan Meier survival curve



The Kaplan Meier survival curve shows the cumulative survival of all the patients in respect to time to analgesic requirement .The above graph shows the existence of post operative analgesia in both the groups .In the P

group 62.9%of the patients had been continuing analgesia upto 6 hours and the remaining 37.1% had been experiencing analgesia upto a period of 8 hours in the post operative period. But the same analgesic effect was present in the N group only upto 4 hours after which there were no patients continuing the analgesia.

Adverse effects

	Group P	**Group N**
Intolerance	0	0
Bleeding	0	0
Epigastric pain	0	0
PONV	0	0

There were no adverse events observed in both the groups.

DISCUSSION

Tonsillectomy [46] is one of the most frequently performed surgical procedures, and its main indication is severe recurrent tonsillitis. The tonsils and adenoids are part of Waldeyer's ring of lymphoid tissue around the pharynx and are often the sites of acute and chronic inflammation. Tonsillectomy and adenoidectomy are not minor procedures; they involve a shared airway, often in a small child, with difficult access, obstructive airway symptoms, and the potential for blood contamination of the lower airway. Mortality associated with tonsillectomy ranges from 1:40,000 to 1:12,000. The provision of adequate analgesia after tonsillectomy presents the anaesthesiologist with difficulties as this is a painful procedure and may be associated with significant bleeding into the airway[2]

Recommended approaches for post operative pain management is to initiate therapy with analgesics such as paracetamol, NSAIDS, aspirin and opioids. Opioids when used to provide effective postoperative analgesia for tonsillectomy may be associated with side effects like sedation, respiratory depression and vomiting[47,48] which may make recovery hazardous after pharyngeal surgery particularly in children. Non-steroidal anti-inflammatory drugs not only produce good analgesia but also avoid the side effects of opioids. Peri-operative use of NSAIDS has been limited because of concerns over increased postoperative bleeding, which has been demonstrated with ketorolac[49,50] although apparently not for other NSAIDS[51]. Paracetamol is an effective analgesic and an antipyretic agent [3,4]. Efficiency and tolerability for Paracetamol are well established[35]. It has a favourable safety profile and it is

the most commonly prescribed drug for the treatment of mild to moderate pain. Recent studies have exposed the role of intravenous (IV) Paracetamol in post-operative pain relief[5,6,7,8,9,10,11,12,13,14,15].

Atef A, Fawaz AA.et al[5] reported that iv paracetamol administered regularly in adult patients with moderate to severe pain after tonsillectomy, provided rapid and effective analgesia and was well tolerated as compared to placebo. The present study also compared the analgesic efficacy and tolerability of IV Paracetamol where in, the administration of 15mg/kg of paracetamol IV provided analgesia upto 6 hours in the post operative period which was superior to placebo in managing postoperative pain.

Alhashemi JA et al[6] compared i.v. acetaminophen 15mg/kg with intramuscular (i.m.) meperidine 1mg/kg in eighty children undergoing tonsillectomy and observed that objective pain score (OPS scores) were 3.1 for the acetaminophen group and 2.1 for the meperidine group (P=0.147); however, Ramsay sedation scores were 3 and 4 for the acetaminophen and meperidine groups, respectively(P<0.05). In the present study also ramsays sedation score was used to compare level of sedation. In the paracetamol group sedation score was 2.9 at the end of surgery,score of 2.6 at the end of first hour,2 at the end of second hour,1.7at the end of 3 hours and after that both the groups were with a mean score of one up to six hours in post operative period. Thus i.v paracetamol produced acceptable sedation in the post operative period without any compromise to the airway.

In another study **T.Alhashemi JA,et al**[7] reported that intraoperative iv paracetamol in comparison with i.m meperidine resulted in higher pain scores but earlier readiness for recovery room discharge in paediatric patients undergoing dental restoration. In the present study, i.v paracetamol had better recovery profile as compared to placebo and better pain relief with no adverse effects.

Mehmet Turan Inal et al[15] compared the quality of analgesia and side effects of iv paracetamol versus meperidine for postoperative analgesia in parturients undergoing elective caesarean section in a randomised double-blind study. In the meperidine group the VAS scores after the operation were higher than paracetamol group. But in the paracetamol group most of the patients had lower VAPS and had the first rescue analgesic six hours after the operation. They concluded that i.v. paracetamol has better analgesic potency than i.v. meperidine for postoperative analgesia after caesarean section. In the present study also there was lower VAPS score in the paracetamol group with the time to first rescue analgesic after a mean duration of 6 hours.

Ahmed Al Fadly et al[11] studied the analgesic effect of intravenous paracetamol, morphine and their combination for post operative pain after release of post burn neck contractures. They concluded that IV paracetamol effectively reduces morphine requirements by 60% or even replace it, with reduced incidence of adverse events and a safer course during postoperative pain management after release of post burn neck contracture in adults. In the present study also there were no adverse events and the time to first rescue

analgesia was significantly longer in the paracetamol group as compared to the placebo group with mean duration of pain relief upto a period of 6 hours.

Cattabriga et al[13] conducted a placebo-controlled, double-blinded, randomized trial to study the efficacy of intravenous paracetamol as an adjunctive analgesic to a tramadol-based background analgesia after cardiac surgery. Postoperative pain was evaluated by visual analog scale. A rescue dose of 2—5 mg of intravenous morphine was administered whenever the VAPS score was greater than 3. Patients who received paracetamol had significantly less pain at rest ($p = 0.0041$, 0.0039, 0.0044, respectively); after this time the two groups did not differ. Paracetamol group required less cumulative morphine than placebo group .They concluded that iv paracetamol in combination with tramadol provides effective pain control. But in the present study, the postoperative pain was evaluated by visual analog scale and a rescue dose of 1.5 mg/kg of i.m diclofenac was administered whenever the VAPS score was greater than 4. Here Iv paracetamol provided effective pain control in the post operative period upto a period of 6 hours.

In the present study, the mean pulse rate at 0 – 6 hours in the post operative period for P group was significantly lower than the N group ($P < 0.001$). The mean MAP at 0 – 6 hrs in the post operative period was significantly higher in N group than P group ($P < 0.001$). These statistics explain the analgesic efficacy of paracetamol which resulted in a stable hemodynamic status. Thus IV Paracetamol produced a better haemodynamic profile in the post-operative period.

Statistically significant conscious sedation was observed in paracetamol group with a score of 2.6 at the end of first hour, 2 at the end of second hour, 1.7 at the end of 3 hours after that both the groups were with a mean score of one up to six hours in post operative period. This explains the analgesic efficacy of paracetamol which rendered the children calm, co-operative and tranquil in the post-operative period. Moreover, paracetamol was well tolerated by the pediatric population and no adverse effects were noted during the study.

SUMMARY

1. **Intravenous Paracetamol** achieved significant post operative pain relief up to 6 hours.
2. **Intravenous Paracetamol** delayed the requirement of first dose of rescue analgesic for a mean duration of 6 hours in the post-operative period.
3. **Intravenous Paracetamol** had a better haemodynamic profile in the post-operative period.
4. **Intraveous Paracetamol** had a smooth and better post-operative recovery profile rendering a calm, co-operative and tranquil patient.
5. **Intravenous Paracetamol** did not exhibit any adverse effects in the patients.

CONCLUSION

1. **Intravenous Paracetamol** can be used as an effective analgesic for providing pre-emptive analgesia.
2. **Intravenous Paracetamol** provides excellent post operative pain relief.
3. **Intraveous Paracetamol** has a better hemodynamic profile.
4. **Intraveous Paracetamol** is safe for use in patients

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PROFORMA

Name: Age: Sex: Wt: kg

Date : I.P. no: ASA:

History :

Investigations :

Hb%: urine albumin:

Blood sugar: sugar:

Urea: deposits:

Creatinine: BT: CT:

O/E

Anaemia: CVS; RS:

PR: BP:

Pre-med : Inj. Midazolam 0.07mg/kg i.m

Inj. Glycopyrrolate 0.004mg/kg i.m. 45 min prior to surgery

Group P : I.V. paracetamol 15mg/kg infusion 15 minutes before the start of the procedure

Group N : Normal saline infusion 100ml 15 minutes

before the start of the procedure

Induction : Inj Fentanyl 2 mcg/kg

Inj.thiopentone 5mg/kg

Inj.rocuronium 0.6 mg/kg

Airway : ETT

Maintenance : O_2 / N_2O / Halothane

Parameters Monitored:

Intra op;

Time in min	Haemodynamic variables		
	PR	MAP	SpO_2
Just after induction (JAI)			
5 min			
15 min			
30min			
End of surgery (EOS)			

Duration of surgery :

Post operative :

Time in hrs	Haemodynamic variables			Sedation score	VAPS
	PR	MAP	SpO_2		
1 hr					
2 hr					
3 hr					
4 hr					
5 hr					
6 hr					

Time to first analgesic requirement :

Side effects : Epigastric pain / Bleeding / Intolerance / PONV

Group P

SNO	NAME	AGE/SEX	WEIGHT	PREOP			DOS	INTRAOP									
								PR					SPO2				
				P	SPO2	BP		JAI	5 MIN	15 MIN	30 MIN	EOS	JAI	5 MIN	15MIN	30MIN	EOS
1	SATHIK	8/M	18kg	100	100	65	45MIN	108	104	104	102	105	100	100	99	100	100
2	MAHESKUMAR	11/M	25KG	94	99	66	45MIN	100	96	97	96	98	99	100	99	99	99
3	FEROZBANU	14/F	25KG	90	99	66	45MIN	98	97	96	95	98	99	100	99	99	99
4	MADHU	6/M	10KG	104	100	66	40MIN	110	108	106	104	100	100	100	99	100	100
5	INDHUMATHI	12/F	25KG	90	99	66	60MIN	100	98	97	96	96	99	100	99	99	99
6	SARASWATHI	10/F	20KG	92	100	66	45MIN	100	98	97	96	97	100	100	99	100	100
7	VIGNSEH	7/M	20KG	100	99	65	50MIN	110	106	106	105	106	99	100	99	99	99
8	ROHINI	13/F	25KG	90	100	66	35MIN	100	98	97	96	100	100	100	99	100	100
9	SABEENA	12/F	30KG	86	99	66	40MIN	96	95	93	92	96	99	100	99	99	99
10	MUTHULAKSMI	8/F	12KG	100	100	65	45MIN	108	106	103	103	105	100	100	99	100	100
11	KARTHIK	12/M	25KG	92	99	66	45MIN	100	98	97	96	96	99	100	99	99	99
12	VIGNESH	16/M	35KG	82	99	65	45MIN	96	94	92	90	94	99	100	99	99	99
13	ABISHA	7/F	20KG	98	99	66	45MIN	106	104	102	100	102	99	100	99	99	99
14	HARI	6/M	15KG	98	99	66	40MIN	107	105	102	100	102	99	100	99	99	99
15	SELVARAJAN	8/M	20KG	98	100	66	40MIN	106	104	102	100	102	100	100	99	100	100
16	SIVANASH	7/M	14KG	100	100	66	35MIN	108	106	104	102	105	100	100	99	100	100
17	SABERNISHA	7/M	20KG	99	100	66	40MIN	107	104	103	102	105	100	100	100	100	100
18	JAMIMA	9/F	15KG	96	100	66	45MIN	104	101	101	100	104	100	100	100	100	100
19	NATCHIAYAR	10/F	25KG	94	99	66	45MIN	99	96	96	98	102	99	99	100	99	99
20	HEMALKUMAR	6/M	12KG	106	99	65	50MIN	108	105	103	103	105	99	100	100	99	99
21	GRACE	6/F	10KG	104	99	65	40MIN	105	103	102	101	105	99	100	100	99	99
22	MUTHULATHA	12/F	25KG	90	100	65	60MIN	100	98	97	96	96	100	100	100	100	100
23	PRAVEEN	10/M	20KG	92	100	65	45MIN	100	98	97	96	97	100	99	100	100	100
24	PRIYA	7/F	14KG	100	100	65	50MIN	107	106	106	105	106	100	99	100	100	100
25	KRISHNA	13/M	25KG	90	100	65	35MIN	100	98	97	96	100	100	99	100	100	100
26	ANDAL	12/F	26KG	86	100	66	40MIN	96	95	93	92	96	100	99	100	100	100
27	SARADHA	8/F	12KG	100	99	66	45MIN	108	107	106	105	105	99	99	100	99	99
28	VISHAL	12/M	22KG	92	99	66	45MIN	100	98	97	96	96	99	99	100	99	99
29	KUMAR	14/M	26KG	82	99	66	45MIN	96	94	92	90	94	99	99	100	99	99
30	ANITHA	7/F	15KG	98	99	66	45MIN	106	104	102	100	102	99	99	100	99	99
31	YASIM	7/F	12KG	100	100	64	35 MIN	106	104	102	100	102	100	99	100	100	100
32	SARNYA	10/F	20KG	96	100	66	45MIN	100	98	97	96	97	100	99	100	100	100
33	YALATHI	10/F	20KG	98	99	65	40MIN	102	100	100	99	95	99	99	100	99	99
34	ESSAKI	11/M	25KG	94	99	65	45MIN	100	98	97	96	96	100	100	100	100	100
35	KALIRAJ	12/M	30KG	87	99	66	40MIN	96	95	93	92	96	99	100	99	99	99

Group P

INTRAOP					POST OPERATIVE HOURS																	
MAP					PR						SPO2						MAP					
JAI	5 MIN	15 MIN	30 MIN	EOS	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
69	68	67	66	67	97	97	98	99	99	103	100	100	99	100	100	100	65	63	65	66	66	68
70	66	65	65	66	95	95	96	96	98	99	100	100	99	99	99	100	65	63	63	66	68	70
70	66	66	65	67	93	93	94	94	95	96	100	100	99	99	99	100	63	64	64	65	67	68
69	68	68	66	67	96	95	96	97	98	100	100	100	99	100	100	100	64	66	66	67	68	68
70	68	67	66	66	94	95	96	96	98	100	100	100	99	99	99	100	64	66	66	67	67	68
70	68	67	66	69	95	96	96	95	97	99	100	100	99	100	100	100	64	66	66	66	67	67
69	68	67	66	70	98	94	98	97	98	99	100	100	99	99	99	100	64	66	66	66	66	68
70	68	67	67	68	96	94	96	96	98	100	100	100	99	100	100	100	62	63	64	65	67	68
69	68	67	67	68	93	92	93	92	94	96	100	100	99	99	99	100	65	66	66	66	67	68
69	68	67	67	67	99	98	99	100	101	103	100	100	99	100	100	100	66	66	66	66	68	68
69	68	65	64	64	92	92	93	92	94	95	100	100	99	99	99	100	62	63	64	64	64	65
69	67	66	69	68	90	90	91	90	93	95	100	100	99	99	99	100	65	65	65	66	67	67
69	67	66	65	65	97	97	98	97	99	100	100	100	99	99	99	100	63	64	64	65	65	66
69	67	66	65	65	96	96	96	97	99	100	100	100	99	99	99	100	63	64	64	64	64	65
69	67	66	65	66	96	97	99	99	100	102	100	100	99	100	100	100	63	65	65	65	67	67
69	68	67	66	66	99	99	100	100	100	103	100	100	99	100	100	100	63	63	63	63	64	66
70	68	67	66	65	99	99	99	100	100	104	100	100	100	100	100	100	63	64	64	64	65	66
69	68	67	66	65	98	99	99	97	98	100	100	100	100	100	100	100	63	64	64	64	64	66
70	69	68	67	65	95	95	96	96	97	99	99	99	100	99	99	99	63	64	64	64	64	66
69	68	67	66	66	97	98	99	100	100	101	100	100	100	99	99	100	63	63	64	64	64	65
70	68	68	67	67	96	97	97	97	99	101	100	100	100	99	99	100	64	64	**64**	65	66	67
70	68	67	67	66	93	95	95	96	98	100	100	100	100	100	100	100	64	64	65	66	67	67
70	68	67	67	69	95	96	96	97	97	99	99	99	100	100	100	99	65	65	65	66	66	67
69	68	67	67	70	85	96	96	97	98	99	99	99	100	100	100	99	66	63	63	65	65	66
70	68	67	67	68	95	95	96	96	98	100	99	99	100	100	100	99	64	66	66	66	66	67
70	68	67	67	68	90	91	92	93	94	96	99	99	100	100	100	99	65	66	67	67	66	67
69	68	67	67	67	99	99	100	102	104	105	99	99	100	99	99	99	64	66	66	66	66	67
70	68	65	62	64	90	90	90	92	94	95	99	99	100	99	99	99	62	63	63	64	64	65
69	67	66	65	68	90	90	90	90	93	95	99	99	100	99	99	99	64	65	65	65	65	68
69	67	66	65	65	97	95	96	97	99	100	99	99	100	99	99	99	63	64	64	64	65	66
68	66	66	65	65	97	97	97	98	99	100	99	99	100	100	100	99	62	64	64	65	66	66
70	68	67	67	69	94	94	95	95	97	99	99	99	100	100	100	99	63	63	64	64	66	66
68	67	66	66	66	90	92	93	93	96	99	99	99	100	99	99	99	63	63	64	64	64	66
70	68	67	67	66	93	94	96	96	98	100	100	100	100	100	100	100	64	66	66	66	67	67
70	68	67	67	68	91	91	92	94	94	96	100	100	99	99	99	100	64	65	66	66	67	67

Group P

POST OPERATIVE HOURS																TIME TO FIRST ANALGESIC REQUIREMENT HOU
SEDS							VAPS									
EOS	1	2	3	4	5	6	EOS	1	2	3	4	5	6	7		
3	3	2	2	1	1	1	0	0	0	1	2	3	4			5.5
3	3	2	2	1	1	1	0	0	0	0	2	3	4			5.25
3	3	2	2	1	1	1	0	0	0	1	2	3	4			5.5
3	3	2	2	1	1	1	0	0	0	1	2	3	4			6
3	3	2	2	1	1	1	0	0	0	1	2	3	4			6
3	3	2	2	1	1	1	0	0	0	1	2	3	4			6
3	3	2	2	1	1	1	0	0	0	1	2	3	4			6
3	3	2	2	1	1	1	0	0	0	1	2	3	4			5.75
3	3	2	2	1	1	1	0	0	0	1	2	3	4			5.75
3	3	2	2	1	1	1	0	0	0	1	2	3	4			6
3	3	2	1	1	1	1	0	0	0	1	2	2	4			6
3	3	2	2	1	1	1	0	0	0	1	1	2	4			6
3	3	2	2	1	1	1	0	0	0	1	1	2	3	4		7
3	3	2	2	1	1	1	0	0	0	1	1	2	3	4		7
2	2	2	1	1	1	1	0	0	0	1	1	2	3	4		6.5
3	2	2	2	1	1	1	0	0	0	1	1	2	3	4		7
3	2	2	2	1	1	1	0	0	0	1	1	2	3	4		6.5
2	2	2	2	1	1	1	0	0	0	1	1	2	3	4		6.25
3	2	2	1	1	1	1	0	0	0	1	1	2	3	4		6.25
3	2	2	2	1	1	1	0	0	0	1	1	2	3	4		7
2	2	2	2	1	1	1	0	0	0	1	1	2	3	4		6.5
3	2	2	2	1	1	1	0	0	0	1	1	2	3	4		6.5
3	2	2	2	1	1	1	0	0	0	1	1	2	3	4		7
3	2	2	2	1	1	1	0	0	0	1	2	3	4			5.5
3	3	2	2	1	1	1	0	0	0	1	2	3	4			5.25
3	2	2	2	1	1	1	0	0	0	1	2	3	4			5.5
3	3	2	1	1	1	1	0	0	0	1	2	3	4			6
3	3	2	2	1	1	1	0	0	0	1	2	3	4			6
3	3	2	1	1	1	1	0	0	0	1	2	3	4			6
3	3	2	1	1	1	1	0	0	0	1	2	3	4			6
3	3	2	1	1	1	1	0	0	0	1	2	3	4			5.75
3	2	2	1	1	1	1	0	0	0	1	1	2	3	4		7
3	3	2	2	1	1	1	0	0	0	1	2	3	4			5.5
3	2	2	1	1	1	1	0	0	0	1	1	2	3	4		5.75
3	3	2	2	1	1	1	0	0	0	1	2	3	4			6

Group N

SNO	NAME	AGE/SEX	WEIGHT	PREOP			DOS	INTRAOP									
								PR					SPO2				
				P	SPO2	BP		JAI	5 MIN	15 MIN	30 MIN	EOS	JAI	5 MIN	15MIN	30MIN	EOS
1	MANOJ	8/M	12KG	100	100	65	45MIN	110	107	106	105	105	100	100	99	100	100
2	KUMAR	11/M	25KG	94	100	67	45MIN	100	96	97	98	96	99	100	99	99	99
3	VALLI	14/F	25KG	90	100	67	45MIN	98	97	96	95	96	99	100	99	99	99
4	KANNAN	6/M	10KG	104	100	66	40MIN	110	108	106	104	100	100	100	99	100	100
5	MUPIDARI	12/F	25KG	90	100	66	60MIN	100	98	97	96	96	99	100	99	99	99
6	GEETHA	10/F	20KG	92	100	65	45MIN	100	98	97	96	97	100	100	99	100	100
7	PETCHI	7/M	20KG	100	100	65	50MIN	110	106	106	105	106	99	100	99	99	99
8	AYESHA	13/F	25KG	90	100	64	35MIN	100	98	97	96	100	100	100	99	100	100
9	NANDHINI	12/F	30KG	86	100	65	40MIN	96	95	93	92	96	99	100	99	99	99
10	MEENA	8/F	12KG	90	100	64	45MIN	109	107	106	105	105	100	100	99	100	100
11	KUMAR	12/M	25KG	92	100	65	45MIN	100	98	97	96	96	99	100	99	99	99
12	KRISHNAN	15/M	32KG	86	100	65	45MIN	96	94	92	90	94	99	100	99	99	99
13	RAJAKUMARI	7/F	20KG	98	100	66	45MIN	106	104	102	100	102	99	100	99	99	99
14	LAKSHMANAN	6/M	15KG	103	100	66	40MIN	107	105	102	100	102	99	100	99	99	99
15	SANTHOSH	8/M	20KG	100	100	65	40MIN	106	104	102	100	102	100	100	99	100	100
16	UYIKATTAN	7/M	20KG	100	100	66	35MIN	110	108	106	104	106	100	100	99	100	100
17	SURYA	7/M	20KG	102	100	66	40MIN	109	106	106	106	108	100	100	100	100	100
18	MERLIN	9/F	16KG	98	100	66	45MIN	107	104	103	102	104	100	100	100	100	100
19	RAJALAKSHNI	10/F	20KG	94	99	65	45MIN	106	105	104	102	105	99	99	100	99	99
20	PIRATHOSH	6/M	10KG	106	100	66	50MIN	108	107	107	106	108	99	100	100	99	99
21	SUDHA	8/F	12KG	104	100	66	40MIN	108	106	108	108	109	99	100	100	99	99
22	VALLI	11/F	25KG	94	100	66	45MIN	100	96	97	98	96	100	100	100	100	100
23	SUMATHI	14/F	30KG	90	99	65	45MIN	98	97	96	95	96	100	99	100	100	100
24	SARADHA	6/F	10KG	104	99	66	40MIN	108	106	105	104	106	100	99	100	100	100
25	ANDAL	12/F	25KG	90	99	66	60MIN	100	98	97	96	96	100	99	100	100	100
26	KUMARAN	10/M	20KG	92	99	66	45MIN	100	98	97	96	97	100	99	100	100	100
27	FAIZ	7/M	15KG	100	99	65	50MIN	110	106	106	105	106	99	99	100	99	99
28	RAJINI	13/M	25KG	90	99	66	35MIN	100	98	97	96	100	99	99	100	99	99
29	KARTHICK	12/M	30KG	86	99	64	40MIN	96	95	93	92	96	99	99	100	99	99
30	KUMAR	8/M	12KG	100	99	66	45MIN	110	107	106	105	105	99	99	100	99	99
31	SYED FATHIMA	13/F	30KG	88	99	66	40MIN	96	94	92	90	94	100	99	100	100	100
32	SARAVANAN	15/M	33KG	88	99	65	45MIN	98	97	96	95	96	100	99	100	100	100
33	RAJABHAVANI	8/F	12KG	100	99	64	35 MIN	107	104	103	102	104	99	99	100	99	99
34	LAKSHMI	10/F	18KG	96	100	65	40MIN	100	98	97	96	97	100	100	100	100	100
35	JOHN	8/M	12KG	100	100	64	45MIN	110	107	106	105	105	99	100	99	99	99

Group N

INTRAOP					POST OPERATIVE HOURS																	
MAP					PR						SPO2						MAP					
JAI	5 MIN	15 MIN	30 MIN	EOS	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
69	68	67	67	69	104	105	107	108	109	110	100	100	100	99	100	100	67	68	68	69	70	70
70	66	65	67	70	95	96	97	98	99	102	99	99	100	99	99	99	66	67	67	68	69	70
70	66	66	67	70	95	96	98	99	102	103	99	99	100	99	99	99	67	68	68	69	70	72
70	68	68	67	70	99	100	104	104	105	106	100	100	100	99	100	100	67	67	67	68	69	70
70	68	67	67	70	96	96	98	99	100	102	99	99	100	99	99	99	66	68	68	70	70	70
70	68	67	67	69	96	97	99	100	101	103	100	100	100	99	100	100	69	70	70	71	72	72
69	68	67	67	69	104	106	107	109	110	111	99	99	100	99	99	99	70	70	70	71	72	72
70	68	67	67	69	99	100	102	103	104	105	100	100	100	99	100	100	68	69	69	70	71	72
70	68	67	67	69	96	96	97	99	100	102	99	99	100	99	99	99	68	68	68	69	70	70
69	68	67	67	69	103	105	107	108	109	110	100	100	100	99	100	100	67	68	68	69	70	70
70	68	66	62	67	94	96	99	100	100	102	99	99	100	99	99	99	66	66	66	66	66	68
70	69	69	69	70	93	94	95	96	97	98	99	99	100	99	99	99	68	68	68	69	69	70
69	67	66	65	69	100	102	105	106	108	108	99	99	100	99	99	99	65	66	66	67	68	68
69	67	66	65	69	100	102	105	106	107	109	99	99	100	99	99	99	67	68	68	68	69	70
69	67	66	65	69	101	103	104	106	107	107	100	100	100	99	100	100	67	68	68	69	69	70
69	68	67	66	70	106	108	108	110	110	111	100	100	100	99	100	100	66	67	67	68	69	70
69	68	67	66	70	106	113	115	117	117	118	100	100	100	100	100	100	65	67	67	67	69	71
69	68	67	66	69	104	104	106	107	110	113	100	100	100	100	100	100	65	66	66	68	68	68
69	69	68	67	70	102	105	105	107	109	110	99	99	99	100	99	99	65	66	66	68	69	69
69	68	67	66	70	108	105	106	107	108	110	99	99	100	100	99	99	66	67	67	68	69	70
69	68	67	66	70	109	104	105	106	106	107	99	99	100	100	99	99	65	66	66	67	68	69
69	66	65	67	70	95	96	97	98	99	102	100	100	100	100	100	100	66	67	67	68	69	70
69	66	66	67	70	96	96	98	99	102	103	100	100	99	100	100	100	67	68	68	69	70	71
70	68	68	67	70	106	100	104	104	105	106	100	100	99	100	100	100	67	67	67	68	69	70
70	68	67	67	70	96	96	99	99	100	102	100	100	99	100	100	100	66	68	68	70	70	70
70	68	67	67	69	97	98	100	100	101	103	100	100	99	100	100	100	69	70	70	70	71	72
69	68	67	67	69	106	99	100	102	104	105	99	99	99	100	99	99	68	69	69	70	71	71
70	68	67	67	70	100	100	102	103	104	105	99	99	99	100	99	99	68	69	69	70	71	72
70	68	67	67	70	96	96	97	99	100	102	99	99	99	100	99	99	68	68	68	69	70	70
69	68	67	67	70	105	100	102	104	105	105	99	99	99	100	99	99	67	68	68	69	70	70
73	72	70	69	70	94	94	95	97	99	100	100	100	99	100	100	100	68	68	68	69	69	70
70	66	66	67	70	96	96	98	99	102	103	100	100	99	100	100	100	67	68	68	69	70	72
69	68	67	66	69	104	102	103	104	105	106	99	99	99	100	99	99	65	66	66	68	68	70
70	68	67	67	70	97	97	99	100	101	103	100	100	100	100	100	100	69	70	70	71	72	72
69	68	67	67	70	105	103	104	104	105	106	99	99	100	99	99	99	67	68	68	69	70	70

Group N

POST OPERATIVE HOURS																
SEDS							VAPS									
EOS	1	2	3	4	5	6	EOS	1	2	3	4	5	6	7	TIME TO FIRST ANALGESIC REQUIREMENT Hours
2	1	1	1	1	1	1	1	2	2	4					2.25
1	1	1	1	1	1	1	1	1	2	4					2.5
2	1	1	1	1	1	1	1	2	2	4					2.5
2	1	1	1	1	1	1	1	2	3	4					2.25
2	1	1	1	1	1	1	1	1	2	4					2.5
2	1	1	1	1	1	1	1	2	2	4					2.25
2	1	1	1	1	1	1	1	2	2	4					3
2	1	1	1	1	1	1	1	1	2	4					3
2	1	1	1	1	1	1	1	2	2	4					2.75
2	1	1	1	1	1	1	1	2	2	4					2.5
2	1	1	1	1	1	1	1	1	2	4					2.5
2	1	1	1	1	1	1	1	2	2	4					2.25
2	1	1	1	1	1	1	1	2	3	4					3
2	1	1	1	1	1	1	1	1	2	4					3
2	1	1	1	1	1	1	1	2	3	4					3
2	1	1	1	1	1	1	1	2	2	4					3
2	1	1	1	1	1	1	1	2	2	4					3
1	1	1	1	1	1	1	1	1	3	4					3
2	1	1	1	1	1	1	1	2	2	4					2.25
2	1	1	1	1	1	1	1	3	2	4					2.25
2	1	1	1	1	1	1	1	2	2	4					2.5
2	1	1	1	1	1	1	1	1	2	4					2.5
2	1	1	1	1	1	1	1	2	3	4					2.5
2	1	1	1	1	1	1	1	2	2	4					3
2	1	1	1	1	1	1	1	1	2	4					3
2	1	1	1	1	1	1	1	2	3	4					3
2	1	1	1	1	1	1	1	2	2	4					3
2	1	1	1	1	1	1	1	1	3	4					2.25
2	1	1	1	1	1	1	1	2	2	4					2.25
2	1	1	1	1	1	1	1	2	2	3					2.5
2	1	1	1	1	1	1	1	2	2	4					2.5
2	1	1	1	1	1	1	1	2	3	4					2.5
2	1	1	1	1	1	1	1	1	2	4					2.25
2	1	1	1	1	1	1	1	2	2	4					2.5
2	1	1	1	1	1	1	1	2	3	4					3