"COMPARISON OF ANALGESIC EFFECT OF LIGNOCAINE AND LIGNOCAINE COMBINED WITH ACETAMINOPHEN IN INTRAVENOUS REGIONAL ANAESTHESIA. A ONE YEAR RANDOMIZED CONTROL TRIAL"

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Endorsement By The Hod/Principal/ Head Of The Institution

This is to certify that the dissertation entitled **"COMPARISON OF ANALGESIC EFFECT OF LIGNOCAINE AND LIGNOCAINE COMBINED WITH ACETAMINOPHEN IN INTRAVENOUS REGIONAL ANAESTHESIA - A ONE YEAR RANDOMIZED CONTROL TRIAL"** is a bonafide research work done by **REG NO. BA0111001.**

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LIST OF ABBREVIATIONS USED

ASA	-	American Society of Anaesthesiologist
CNS	-	Central nervous system
COX	-	Cyclooxygenase
CYP1A2	-	Isoenzyme of cytochrome P450
CYP2D6	-	Isoenzyme of cytochrome P450
CYP2E1	-	Isoenzyme of cytochrome P450.
EMLA	-	Eutectic mixture of local anaesthetic
F	-	Female
g	-	Gram
GSH	-	glutathione
GA	-	General Anaesthesia
h	-	Hour
Hb	-	Haemoglobin
HR	-	Heart rate
IM	-	Intramuscular
IV	-	Intravenous
IP / OP No.	-	In Patient / Out Patient Number
IV	-	Intravenous
IVRA	-	Intravenous regional anaesthesia
LA	-	Local Anaesthetic
Kg	-	Kilogram
M	-	Male
Mg	-	Milligram

Mmol	-	Millimoles
Min	-	Minute
ml	-	Milli litre
NAPQI	-	N-acetyl P-benzo-quinone imine
ng	-	Nanogram
NIBP	-	Non invasive blood pressure
NSAID’s	-	Nonsteroidal anti inflammatory drugs
ORIF	-	Open reduction internal fixation
P	-	probability
PACU	-	Post anaesthetic care unit
S.D.	-	Standard deviation
VAS	-	Visual analog scale
µg	-	Microgram

ABSTRACT

Background

Intravenous regional anesthesia (IVRA) is commonly used anaesthetic technique for surgeries of extremities where local anesthetic is deposited intravenously into an exanguinated limb. IVRA was first introduced by August Bier in 1908. IVRA is safe, technically simple, and cost effective compared to general anaesthesia.

Objectives:

To compare the analgesic efficacy of Lignocaine alone versus combination of Lignocaine with Acetaminophen when used in IVRA as related to the onset of sensory blockade and to note the onset of tourniquet pain.

Methodology:

This one year hospital based randomized clinical study was conducted from January 2012 to December 2012 in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, on 60 patients, undergoing elective upper limb surgeries. Patients were distributed into two groups of 30 each i.e. Group I (Lignocaine and Normal saline) and Group II (Lignocaine and acetaminophen).

Results

Mean weight in group I was 68.9 kg and in group II was 66.4 k. Mean age in group I was 39.6 years and in group II was 36.7 years and mean duration of surgery in

group I was 48.9 minutes and in group II was 52.3 minutes. Both the groups were comparable with respect to weight , age and duration of surgery.

Mean duration of onset of sensory blockade in group I was 4.6 minutes and in group II was 1.9 minutes.

Mean duration of onset of tourniquet pain in group I was 26.3 and in group II was 27.8 minutes.

Conclusion:

The results obtained from this study suggest that, the addition of Acetaminophen to Lignocaine in IVRA significantly reduces the onset time of sensory blockade.

Keywords

Lignocaine, IVRA, Acetaminophen, sensory blockade, tourniquet pain.

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INTRODUCTION

Intravenous regional anesthesia (IVRA) is commonly used anaesthetic technique for surgeries of extremities where a local anesthetic is deposited intravenously into exanguinated limb.

IVRA was first introduced by August Bier in 1908. He used an Esmarch bandage to exsanguinate the arm and injected procaine between two constricting bands to produce analgesic effects in the site. This procedure was later simplified in 1931by substituting the surgical cut down with percutaneous vein puncture.[1]

IVRA is safe, technically simple, and cost effective procedure compared to general anaesthesia[2] with success rates of 94 to 98% for upper limb surgeries with additional advantage of providing bloodless field during surgery.[3]

However it is associated with limitations such as systemic toxicity, slow onset, tourniquet pain and inability to provide postoperative analgesia. To overcome these limitations various modalities and adjuvants to local anaesthetics have been tried, with limited success.[4]

Acetaminophen has been a cornerstone of the management of mild to moderate pain and the treatment of fever for more than 50 years. For long it was available in only oral and rectal dosage formulations and its use in the perioperative period was limited. An intravenous (IV) preparation of Acetaminophen is a relatively newer drug formulation having both analgesic and antipyretic property.

The analgesic effect of Acetaminophen may be attributed to decrease in peripheral prostaglandin release, centrally mediated action, COX 2 inhibition and activation of descending serotonergic pathways.[5]

Several studies have proven intravenous acetaminophen as a safe and effective drug in treating mild to moderate pain and as a component of multimodal analgesia.

However there is a inadequate literature regarding the role of acetaminophen as an adjuvant when added to Lignocaine for IVRA.

This study was conducted to evaluate the effect of intravenous acetaminophen on the onset of sensory blockade and tourniquet pain when added to lignocaine for IVRA.

OBJECTIVES

To compare the analgesic effect of Lignocaine alone versus combination of Lignocaine with a Acetaminophen when used in IVRA with respect to

1. Onset of sensory blockade.
2. Onset of tourniquet time.

REVIEW OF LITERATURE

IVRA was first introduced by August Bier in 1908. He used an Esmarch bandage to exsanguinate the arm and injected procaine to produce analgesic effects in the site. The procedure was termed as 'Direct vein anesthesia'.

In 1931 Morrison improved the technique by using a single tourniquet method. In 1963 Holme's modified Bier's block by Lignocaine instead of Procaine and used two individual sphygmomanometer cuffs on the arm. In 1964 Hoyle advocated use of a double ballooned sphygmomanometer cuffs, as a refinement of Holme's technique.[1]

IVRA is a form of regional anaesthesia for outpatient procedures, requiring inexpensive equipment, little preparation, reasonable technical skills with onset time of approximately ten minutes, reliable and safe local anaesthetic technique. It is ideal for short operative procedures on the extremities.[2]

Its limitations include the LA toxicity ,slow onset, tourniquet pain and minimal post-operative analgesia. Therefore adjuvants to LA for IVRA have been proposed to enhance the quality of anaesthesia, tourniquet tolerance and post operative analgesia.

The ideal IVRA solution should have the following features: rapid onset, reduced dose of LA, reduced tourniquet pain and prolonged postdeflation analgesia. At present this can be achieved by the addition of adjuncts like Opioids, Tramadol, Nonsteroidal anti-inflammatory drugs, Dexmedetomidine, Muscle relaxants, alkalinization with Sodium bicarbonate, Potassium and altering temperature of local anaesthetics.[4]

A study conducted to compare the clinical outcome and cost analysis of three anaesthetic techniques-General anaesthesia, IVRA and Axillary block demonstrated that regional anaesthesia was associated with more favourable patient recovery profile than general anaesthesia. Incidence of nausea and vomiting were less and residual analgesia was longer lasting in the post anaesthesia care unit and day care surgery unit. Axillary block associated with longer induction time than general anaesthesia and IVRA. Reduction of nursing time with IVRA was most significant in the recovery period resulting in nursing time and cost saving of 30% in comparison with the general anaesthesia technique.[6]

IVRA is a simple and very effective technique, however various side effects and complications have been reported which are essentially related to the systemic pharmacologic effects of the local anaesthetic agent used.

Radiocontrast studies have demonstrated anaesthetic solution leakage even under correctly positioned and inflated tourniquets, since venous pressure during injection exceeds tourniquet pressure causing passage of drug into the general circulation. This had lead to the complications such as seizures and cardiac arrest.[7]

For implementation of improved safety, a feature has been added in the next generation of automated IVRA, namely a biomedical sensor, which is housed in the cuff. The device is particularly sensitive to cuff artifacts arising from variations in cuff wrap tightness and folding of the cuff. As such, it offers some promise for detecting potentially hazardous conditions which can occur during conventional IVRA procedures. Device still has significant challenges to overcome, in relation to device compliance and poor reproducibility.[8]

Sztark et al made an attempt to reduce the Local anaesthetic toxicity in IVRA by adding Fentanyl $1\mu gkg^{-1}$ and Pancuronium 0.5mg to the Local anaesthetic solution of $1.5mgkg^{-1}$ as 0.25% Lignocaine solution instead of the usual $3mgkg^{-1}$ .This combination produced the same quality of anaesthesia as the 0.5% Lignocaine solution but the dose of local anaesthetic for IVRA was reduced to nontoxic level for the same quality of analgesia. However there was no improvement in postoperative analgesia and short delay in onset of sensory and motor block were noted.[9]

Ropivacaine a newer amide local anaesthetic, is structurally related to bupivacaine with longer duration of action, however, ropivacaine causes less depression of cardiac conduction, presumably because it is a pure s-enantiomer.

Hartmannsgruber et al conducted a study comparing 40 ml of 0.2% Ropivacaine and 0.5% Lignocaine for IVRA and found that there was lower incidence, duration and incidence of CNS side effects. IVRA with Ropivacaine 0.2% provided anesthesia and motor blockade of similar onset and intensity as IVRA with Lidocaine 0.5%, but did not prolong tourniquet tolerance. It provided longer duration of post-tourniquet sensory block which was attributed to more complete and persistent binding of the drug and slow release into the systemic circulation.[10]

Tourniquet pain is a traditional limitation of IVRA. It manifests itself as a dull and aching pain sensation increasing in severity with duration of inflation despite an adequate regional anaesthesia. Even with double tourniquets pain is typically present by 40 min after initial inflation. Theories regarding etiology of tourniquet pain support that the nerve ischemia and compression are the main causes of pain.[7]

A study conducted comparing the effect of EMLA cream, subcutaneous ring anaesthesia and double cuff technique, they found that EMLA and subcutaneous ring anaesthesia provided a predominantly superficial and limited analgesia, whereas double cuff tourniquet provided more reliable analgesia at tourniquet site.[11]

Application of forearm rescue cuff 30 minutes after inflation of arm tourniquet was better tolerated than the arm cuff (49±15 versus 29±11) and associated with lower pain scores following longer tourniquet times and shorter duration of side effects. But it has been regarded as controversial because it may not adequately compress interosseous arteries and may result in greater incidence of intravascular leakage.[12]

A study was conducted using Ketorolac as an adjuvant to lidocaine in IVRA concluded that it provided better control of intraoperative tourniquet pain, improved analgesia in the PACU during the first postoperative hour and diminished the need for analgesic supplements during the first postoperative day.[13]

Another study conducted by Steinberg el al to know the Dose-Response relationship of the ketorolac as component of IVRA with lidocaine. Study found that the optimal dose of ketorolac in IVRA was 20 mg and inceasing the dose to 30 or 60 mg did not affect the duration of postoperative analgesia or analgesic requirement.[14]

In other study to reduce tourniquet pain, lignocaine priming was done with $1mgkg^{-1}$ IV 5 min before IVRA and thereafter $3mgkg^{-1}$ Lignocaine was injected into the isolated and exsanguinated arm, the tourniquet pain was consistently reduced only during distal tourniquet cuff inflation. Whether the statistically significant results are ultimately clinically significant is unclear.[15]

One more limitation of IVRA is the lack of postoperative pain relief after tourniquet deflation because of the rapid washout of anaesthetic solution in gereral circulation.

Sen et al conducted a study with thirty ASA physical status I-II patients scheduled for hand or forearm surgery. IVRA was administered with 3mg/kg 2% lidocaine diluted with saline in the control group or with 200 µg NTG with 3mg/kg lidocaine in NTG group. Study concluded that addition of NTG shortened sensory and motor block onset times, prolonged sensory and motor block recovery times and improved tourniquet pain while prolonging the time for the first analgesic requirement.[4]

Siddiqui et al conducted a study using Tramadol as an adjuvant to IVRA. Patients in each group received 0.5% Lignocaine 40ml plus 2ml of a study solution containing either isotonic saline in the control group or Tramadol 50mg in the group T_{50} or Tramadol 100mg in the group $T_{100.}$ Study confirmed that Tramadol 100mg was the effective dose that shortened the onset of sensory block, improved patients tolerance of tourniquet and reduced the intraoperative analgesic consumption.[16]

A study was conducted to evalute the effects of magnesium sulfate when added to 3mg/kg lignocaine 0.5% in 40 ml solution for IVRA and demonstrated decreased intraoperative fentanyl consumption and pain associated with tourniquet, shortened sensory and motor block, prolonging the time to first postoperative analgesic requirement.[17]

M.C.B. Santhosh et al conducted a study to evaluate the usefulness of addition of fentanyl (0.05 mg) and vecuronium (0.5 mg) to 0.25% lidocaine and to compare it

with 0.5% lidocaine alone in intravenous regional anesthesia for upper limb orthopedic surgeries. There was 100% successful anesthesia in both the groups using a combination of a nontoxic dose of lidocaine, low dose of vecuronium and fentanyl. Thus addition of fentanyl and vecuronium to lidocaine helped in reducing lidocaine dose and, thus, lessening the potential local anesthetic toxicity in IVRA.[18]

Forty ASA I or II patients scheduled for elective upper limb body surface surgery. Biers block was achieved using lidocaine into which either dexmedetomidine 1µg/kg or clonidine 1µg/kg was added. There was no significant difference between two groups regarding onset or regression of both sensory or motor blockade but intraoperatively there was a significant reduction in the number of patients requiring fentanyl analgesia and its consumed amount in dexmedetomidine group (0% & 0µg, respectively) compared to the clonidine group (40% &27±43µg, respectively).Similarly, in the post-operative period there was significant reduction in number of patients requiring analgesia in dexmedetomidine group (5% & 2.5±11µg, respectively) compared to clonidine group (35% and 32±24.5µg, respectively). The quality of anaesthesia was significantly better in dexmedetomidine group compared to clonidine group. Thus study revealed that, adding dexmedetomidine to lignocaine during Bier's block is better than adding clonidine. It also concluded that using 1µg/kg of dexmedetomidine produced more postoperative sedation than 0.5µg/kg[19]

Acetaminophen has very little anti-inflammatory activity, and studies suggest that the possibility of the site of its antinociceptive effect may be in the central nervous system. However several studies have also demonstrated peripheral antinociceptive properties of Acetaminophen in different pain models.

Study conducted by Sen et al to evaluate the effect on pain relief when Acetaminophen was added to Lignocaine for IVRA in patients scheduled for hand surgeries . This study was done taking 3 groups comparing with iv acetaminophen[9]and concluded that there was decreased tourniquet pain , increased aneasthesia quality and decreased postoperative analgesic consumption in group which received acetaminophen with lignocaine in IVRA.[20]

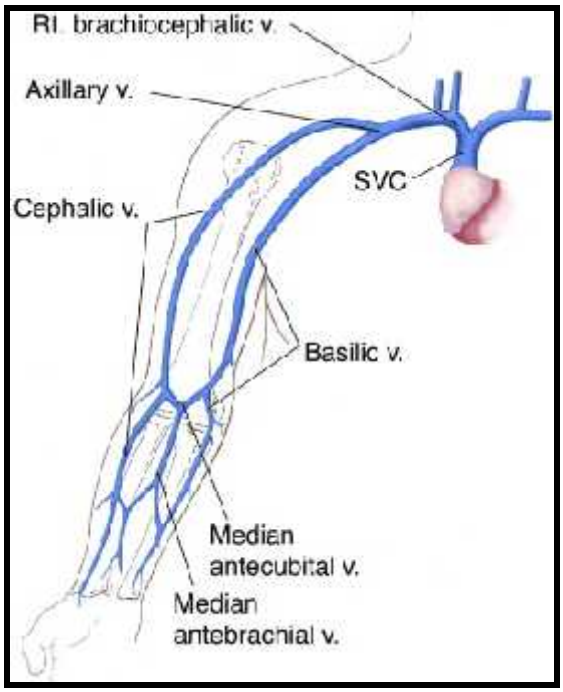
Celik conducted study to know the analgesic effect of Acetaminophen when addeded to Lignocaine for IVRA. He found no difference in sensory and motor block onset and recovery times but improved the postoperative analgesia.[5]

Here in our study we compared two groups, Lignocaine and Normal saline in group I and Lignocaine and Acetaminophen group II for IVRA. However the existing data of Paracetomol as an adjuvant for IVRA are limited and conflicting.

Hence an attempt in this was done to compare the effect of adding Acetaminophen as an adjuvant to Lignocaine in IVRA during upper limb surgeries.

APPLIED BASIC SCIENCES:

Figures -1.VENOUS DRAINAGE OF THE UPPER LIMB



Venous drainage of the upper limb comprises of superficial and deep groups of vessels.

Superficial veins are Cephalic, Basilic, Median cubital vein and their tributaries and are present in the superficial fascia.

Deep group of veins accompany the arteries, these are usually Venae comitantes. They drain the tissues beneath the deep fascia of the upper limb and are connected to the superficial system by perforating veins.

Dorsal digital veins pass along the sides of the fingers and are joined to one another by oblique communicating branches, those from the adjacent sides of fingers unite to form three dorsal metacarpal veins, which forms dorsal venous network at 2-3cm proximal to metacarpophalangeal joint. The radial side network is joined by

dorsal digital vein from radial side of the index finger and dorsal digital veins of thumb and continues proximally as cephalic vein.

The ulnar side of network receives digital veins of the ulnar side of the little finger and is continued upwards as a basilic vein. A communicating branch frequently connects the dorsal venous network with cephalic vein at the middle of the forearm.

The Cephalic vein begins at the radial extremity of the arch, ascends along the lateral aspect of the arm within the superficial fascia and then pierces the deep fascia to enter the axillary vein just distal to the clavicle.

The Basilic vein drains the ulnar end of the arch, passes along the medial aspect of forearm, pierces the deep fascia at the elbow and joins the venae comitantes of the brachial artery to form the Axillary vein. In front of elbow the prominent Median cubital vein links the Cephalic and Basilic veins.It receives number of tributaries from the front of the forearm and gives off the deep median vein which pierces the fascial roof of the antecubital fossa to join the venae comitantes of the brachial artery.

The deep group of veins accompany the arteries, usually as venae comitantes. They are arranged in pairs situated one on each side of the corresponding artery and connected at intervals by the short transverse branches, as most of blood which supplies the upper limb is returned by superficial veins, the deep veins are small and inconspicuous.

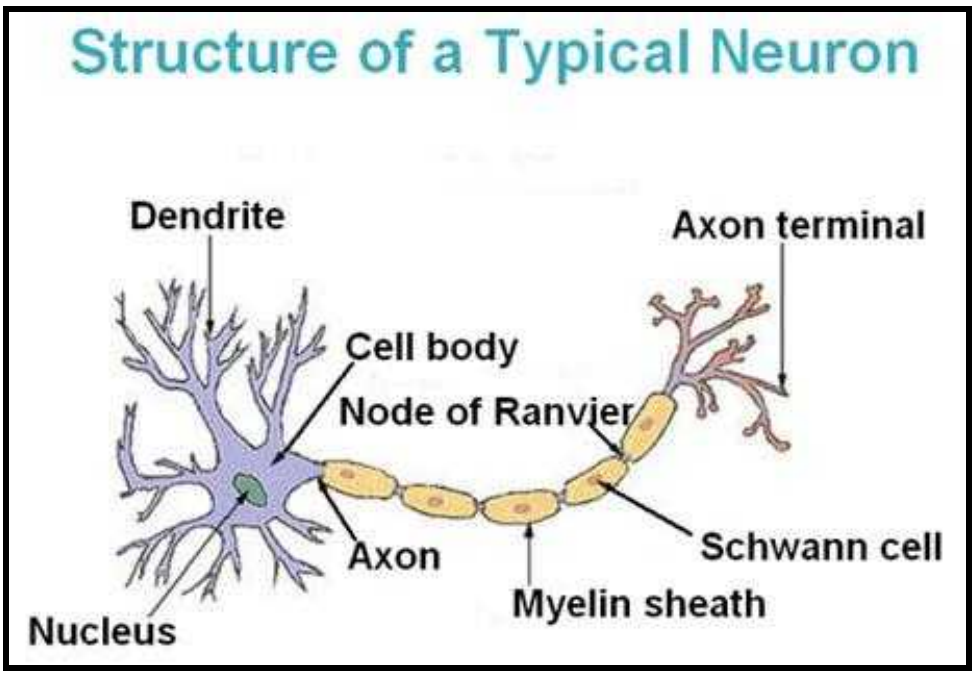
Median vein of forearm drains from palmar surface of hand, it ascends on the front of the forearm and ends in the basilic vein or median cubital vein. In few cases it divides below the elbow into two branches ,one of which joins basilic vein and the

other cephalic vein. In the cubital fossa, the median cubital vein crosses in front of brachial artery and median nerves but is separated from them by bicipital aponeurosis.[23]

Applied anatomy

At the elbow, the median and ulnar nerves are fairly close together and surrounded by large venous channels. The radial nerve is posterolateral and has fewer large vessels near it. Histologically the peripheral nerve shows a thick perineurium, but with many vascular channels in the core of the nerve in close proximity to the nerve fibrils. The greater number of venous channels close to the median and ulnar nerves, compared with the radial nerve, would explain the earlier onset of analgesia on the anteromedial aspect of the forearm.[1]

Figures -2. PHYSIOLOGY OF NERVE CONDUCTION



A neuron consists of a cell body or soma, dendrites, and a nerve fiber or axon. Neuron has five to seven processes called dendrites that extend outward from the cell

body and arborize extensively. Particularly in the cerebral and cerebellar cortex, the dendrites have small knobby projections called dendritic spines. A typical neuron also has a long fibrous axon that originates from a thickened area of the cell body, the axon hillock. The first portion of the axon is called the initial segment. The axon divides into terminal branches, each ending in a number of synaptic knobs. The knobs are also called terminal buttons or axon telodendria. They contain granules or vesicles in which the synaptic transmitters secreted by the nerves are stored.

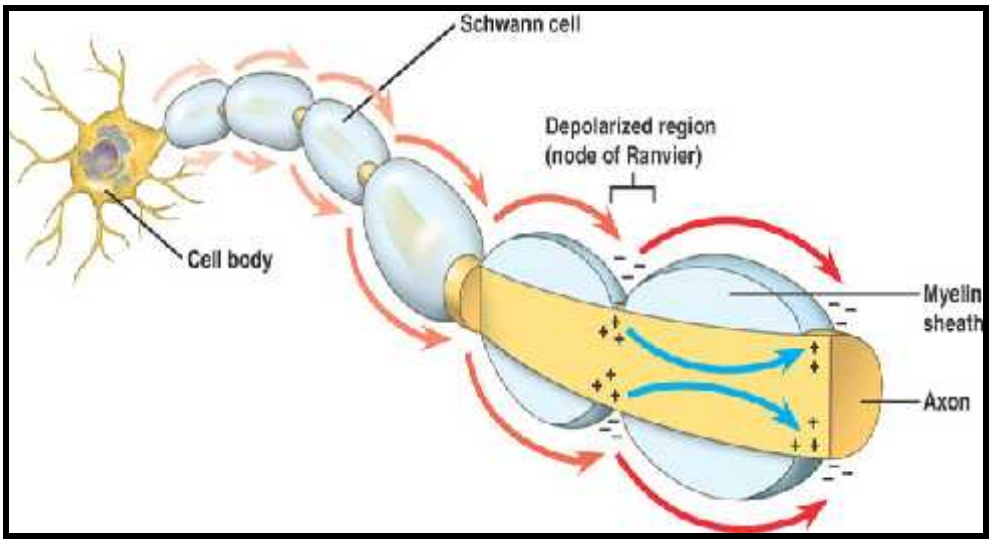
The axons of many neurons are myelinated, i.e., they acquire a sheath of myelin, a protein-lipid complex that is wrapped around the axon. Outside the CNS, the myelin is produced by Schwann cells, glia-like cells found along the axon. The myelin sheath envelopes the axon except at its ending and at the nodes of Ranvier. Not all mammalian neurons are myelinated; some are unmyelinated, ie, are simply surrounded by Schwann cells without the wrapping of the Schwann cell membrane around the axon that produces myelin.

In the CNS of mammals, most neurons are myelinated, but the cells that form the myelin are oligodendrogliocytes rather than Schwann cells. Unlike the Schwann cell, which forms the myelin between two nodes of Ranvier on a single neuron, oligodendrogliocytes send off multiple processes that form myelin on many neighboring axons.

A typical peripheral nerve consists of several axon bundles of fascicles, each fiber has its own connective tissue covering called endoneurium, and each fascicle of axons is covered by perineurium and entire nerve by outer sheath called epineurium. Each peripheral nerve axon has its own cell membrane the axolemma, nonmyelinated nerves contain many axons encased in single Schwann cell sheath.

Myelinated nerve fibres are enclosed in many layers of myelin that wraps around axon. Myelin greatly increases the speed of nerve conduction by insulating the axolemma from the surrounding conducting salt medium and forcing the action current to flow through axoplasm to the nodes of Ranvier, which are periodic interruptions in myelin sheaths, ions can flow freely between nerve fibers and extracellular fluid at the nodes of Ranvier, action potential is transmitted from node to node by myelinated nerve rather than continuously along the entire fibers as occurs in unmyelinated nerve fibers. This successive excitation of nodes of Ranvier by an impulse that jumps between successive nodes is termed **Saltatory excitation**. Saltatory conduction greatly increases velocity of nerve transmission in myelinated fibers.

Figures -3. SALTATORY CONDUCTION



Neural membrane is able to maintain a voltage difference of -60 to -90 millivolts between its inner and outer aspects because at rest it is selectively impermeable to sodium ions but selectively permeable to potassium ions. An active energy dependent Na+ / K+ pump maintains the ion gradients that drive this potential

difference by constant extrusion of sodium from within cell in exchange for net uptake of potassium by using ATP. Intracellular to extracellular K+ ratio of 30:1 is maintained, the nerve at rest behaves as a potassium electrode.

Nerve signals are transmitted by action potentials, which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and then ends with an almost equally rapid change back to the negative potential.[24]

The successive stages of the action potential are as follows:-

Resting Stage: This is the resting membrane potential before the action potential begins. The membrane is said to be "polarized" during this stage because of the –90 millivolts negative membrane potential that is present.

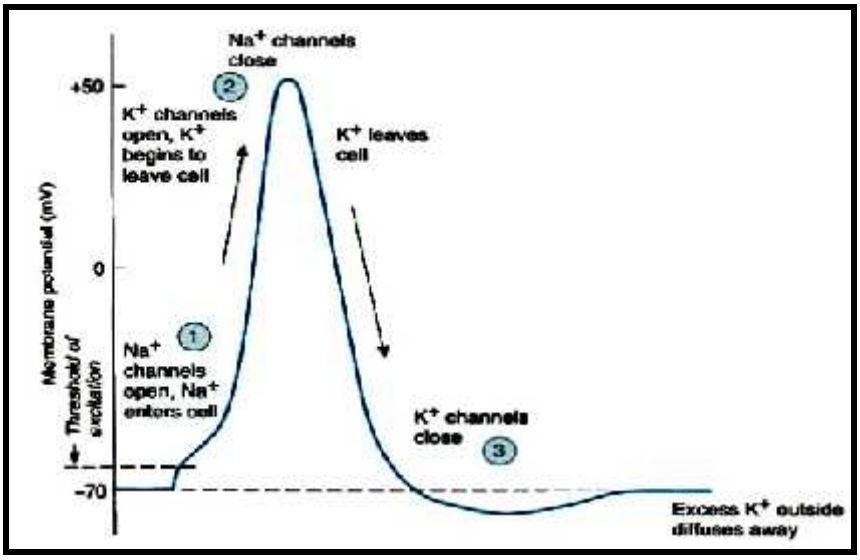
Depolarization Stage. At this time, the membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon. The normal "polarized" state of –90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called depolarization.

Repolarization Stage: Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than normal. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called repolarization of the membrane.[25]

During action potential the nerve membrane transiently switches its permeability from K+ selective to Na+ selective thus changing the membrane potential from negative to positive. and back again, the progress of these potential changes provides basis for understanding of LA conduction blockade.

Impulse is wave of depolarization that is porpogated along the axon by continuous coupling between excited and non excited regions of the membrane. The ionic current entering the axon in the excited, depolarized region flows down the axoplasm and exits through the surrounding membrane thus passively depolarizing the adjacent region.

Although this local circuit current flows away from excited zone in both directions, the region behind the impulse having just been depolarized is absolutely refractory and impulse propogation is thus unidirectional.[24]



CLASSIFICATION OF NERVES

Fibre	Myelinated	Fibre diameter in mm	Conduction velocity m/s	Function
A alpha	Yes	12-20	70-120	Innervation of skeletal muscles, proprioception.
Beta	Yes	5 – 12	30 – 70	Touch, pressure
Gamma	Yes	3 – 6	15 – 30	Skeletal muscle tone
Delta	Yes	2 – 5	12 – 30	Fast pain, touch, temperature
B	Yes	3	3 – 15	Preganglionic autonomic fibres
C	No	0.4 – 1.2	0.5 – 2.0	Slow pain, touch, temperature, postganglionic symphathetic fibres.

Site and mechanism of action in IVRA

Despite vast clinical experience and success with IVRA, the site and mode of action of LA agent in IVRA are still controversial. It is possible that the local anaesthetics act at two levels. First at the level of the nerve endings and secondly at the level of the nerve trunks themselves.

Since the venous system is a one way flow system due to valves, an anaesthetic solution injected into a superficial vein travels proximally from the site of

injection to the level of the applied tourniquet. Initially, the solution fills the large superficial veins: radial, ulnar and median antebrachial. As the full volume of solution is introduced, it concentrates in the region of the elbow, particularly in the anterior part, filling the anticubital veins. This is reasonable since there are large veins about the elbow with minimal resistance, small veins in the muscles, deep veins and perforating veins are filled later. Venous channels distal to the site of injection and towards the fingers are poorly filled. Some diffusion via perforating veins to the interosseous veins also occurs.

After filling the venous channels around the elbow, which are in proximity to main nerve trunks, smaller vascular channels take the agent to the core of the nerve trunks. Once in the core, the local anaesthetic diffuses towards the periphery of the nerve.[26]

LIGNOCAINE

Lignocaine was synthesized by Lofgren in Sweden in 1943. Anaesthetic properties of lignocaine were discovered in 1948 by Lofgren and Lundquist. It was introduced into clinical practice by Gordh in 1949. It is an amide type of local anaesthetic. It also has anti-arrhythmic action apart from its local anaesthetic action.

CHEMICAL STRUCTURE.

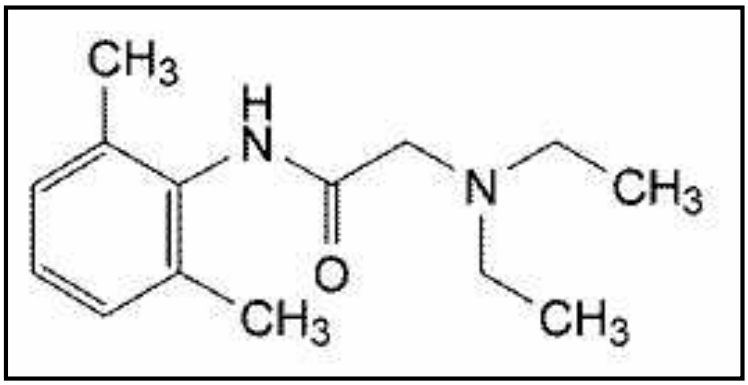


Figure -4: Lignocaine Chemical Structure

Lignocaine is grouped under amides of amino acids with aromatic amines-aminoacylamides (N-diethyl amino acetyl 2, 6, xylidine hydrochloride monohydrate). It contains a tertiary amine attached to an aromatic system by an intermediate chain. The tertiary amine is the base. The chain contains amide linkage. The aromatic ring is lipophilic, where as the tertiary amine end is relatively hydrophilic, Lignocaine is 65% protonated at pH 7.4.

Molecular weight of the base is 234 and that of hydrochloride salt is 270, pKa at 25 degree Celsius is 7.9, partial coefficient is 29 and protein binding 64%. It is stable and not decomposed by heat and alkali. It is having moderate potency and good penetration as a local anaesthetic.

MECHANISM OF ACTION

The action of the local anaesthetic is on the cell membrane of the axon on which it produces electrical stabilization. The large transient increase in the permeability to sodium ions, necessary for propagation of the impulse is prevented, thus the resting membrane potential is maintained and depolarization in response to stimulation is inhibited. Threshold for electrical stimulation is raised, rate of rise of action potential reduced and conduction closed, eventually propagation fails.

Local anaesthetics block the sodium conductance probably by a dual action on the cell membrane.

1. They act directly on receptors within the sodium channels.
2. They produce non-specific membrane expansion.

ACTION ON SODIUM CHANNELS

This action accounts for about 90% of the nerve blocking effect. Diffusion of the drug is a function of tissue binding and removal is by the circulation. The local anaesthetic permeates the axon membrane and equilibrates with axoplasm. The speed and the extent of these processes depend on particular drug's pka and lipophilicity of its base and cation species. It blocks the voltage gated sodium channels by inhibiting conformational changes that underline channel activation. It causes both phasic (frequency dependent) and tonic (resting) inhibition.

MEMBRANE EXPANSION

This is a non-specific action and analogous to the electrical stabilization produced by a number of nonpolar, lipid soluble substances such as non ionized

barbiturates and general anaesthesics. There is 3.5% expansion of the membrane volume but the actual volume of the anaesthetic occupying the membrane however is only about 0.3% or less. So, a number of mechanisms have been suggested for membrane expansion. The most likely one is that there is an unfolding of membrane proteins together with a disordering of the lipid component of the membrane, with consequent obstruction of the sodium channel. Displacement of the membrane bound calcium channel may also be involved.

PHARMACOKINETICS:

Lignocaine is poorly absorbed orally (35%), but intramuscular injections result in peak levels within 30 minutes. Protein binding is 33% to 66% and tissue distribution is predominantly to the highly perfused tissues, volume of distribution is $1.7Lkg^{-1}$, $t_{½}$ α-1 minute, $t_{½}$ β-9.6 minute, $t_{½}$ γ-1.6 hr, and clearance 0.95L/min.

It is metabolized in liver by microsomal enzymes. The initial reaction in this process is dealkylation of lignocaine in the following sequence….

1. Monoethylglycine ⟶ Xylidide (MEGX)

2. The second product of major pathway of metabolism is formation of 2, 6-xylidine.

3. This is further metabolized by hydroxylation of the ring structure which is conjugated forming 4-hydroxy 2, 6-xylidine which is the major urinary metabolite.

4. A minor pathway which gives the metabolite monoethylglycine-xylidide to glycine- xylidide.

Both the end products of metabolism are recognized to have anti arrhythmic properties which are equivalent to lignocaine. The toxic effects may be due to these

products. Glycine-xylidide appears to have central effects. It causes headache and altered mental performance. It also potentiates the convulsive activity of monoethylglycine-xylidide and has central nervous system depressant activity.

PHARMACODYNAMICS

Central nervous system

Initial symptoms of LA induced CNS toxicity are feeling of light headedness, dizziness followed frequently by visual and auditory disturbances such as difficulty in focusing, tinnitus and other subjective symptoms include disorientation and feeling of drowsiness.

Objective signs are excitatory in nature like muscular twitching, shivering, and tremors involving muscles of face and extremities ultimately tonic and clonic seizures.CNS excitation is result of an intial blockade of inhibitory pathways in the cerebral cortex by LA, leaving facilitatory nuerons to function in an unopposed fashion, further increase in the dose of LA leads to inhibition of both inhibitory and excitatory circuits leading to generalized CNS depression.

Cardiovascular system

Primary site of action is myocardium where, decrease in electrical excitability, conduction, rate and force of contraction occurs.

Direct Cardiac Effects: Decrease in rate of depolarization of fast conducting purkinje fibers and ventricular muscle. All LA exert dose dependent negative ionotropic action on cardiac muscle. Depression of myocardial contractility is also affected by calcium influx.

Direct peripheral vascular effects: Low doses decrease peripheral blood flow whereas high doses increases blood flow.

Neuromuscular junction and ganglionic synapse

LA affect transmission at the neuromuscular junction and at autonomic ganglia. These are due to block of an ion channel of acetylcholine receptor by high concentration of LA.

Hypersensitivity to LA

Manifest as a allergic dermatitis or a typical asthmatic attack. Hypersensitivity is due to preservative used such as methylparaben that may provoke allergic reaction, other reason is contamination of vials with latex antigen.

TOXICITY OF LIGNOCAINE	
Serum level	**Clinical effect/Toxic effect.**
2 $\mu g ml^{-1}$	Antiarrhythmic.
3 $\mu g ml^{-1}$	Perioral and tongue numbness.
4 $\mu g ml^{-1}$	Light headedness and tinnitus.
6 $\mu g ml^{-1}$	Visual disturbances.
8 $\mu g ml^{-1}$	Muscle twitching
10 $\mu g ml^{-1}$	Convulsion
12 $\mu g ml^{-1}$	Unconsciousness
15 $\mu g ml^{-1}$	Coma
20 $\mu g ml^{-1}$	Respiratory arrest
25 $\mu g ml^{-1}$	Cardiovascular depression.

CLINICAL APPLICATIONS OF LIGNOCAINE

1. **Infiltration anaeshesia:** Injection of LA directly into tissues without taking into consideration the course of cutaneous nerves.

2. **Field block anaesthesia:** Is subcutaneous injection of a solution of LA in manner to anaesthetise the region distal to the injection site.

3. **Topical anaeshesia:** By direct application of aqueous solution of salts of LA or suspension of poorly soluble LA.

4. **Nerve block anaesthesia:** Injection of LA into or about individual peripheral nerves or nerve plexuses. The four major determinants of onset of anaesthesia are 1) proximity of injection to nerve. 2) concentration and volume of drug 3) ionization of drug 4) Time of injection

5. **IVRA:** The technique lies on using the vasculature to bring the LA solution to the nerve trunks and nerve endings.

6. **Spinal anaesthesia:** Injection of LA into CSF in the subarachnoid space.

7. **Epidural anaesthesia:** Injection of LA into epidural space, epidural catheter can be passed and the technique can be used for prolonged surgeries and postoperative analgesia.

8. **Systemic LA for neuropathic pain:** Variety of LA, antiarrhythmics, anticonvulsants and other Na+ channel blockers are administered IV and orally to relieve neuropathic pain.[27,28]

PRECAUTION TO BE TAKEN DURING LIGNOCAINE USAGE

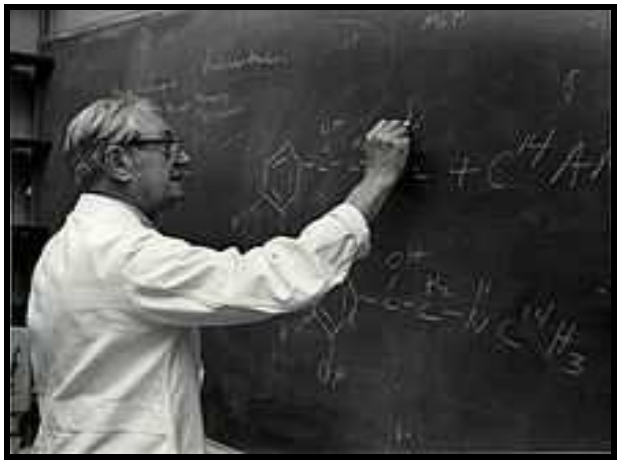
1. ECG monitoring for intravenous administration.
2. During epidural anaesthesia a test dose is recommended.
3. Should be used with caution in advanced heart failure, Hepatic disease, Hypovolemia, Heart block, Stokes Adams syndrome, Shock, Renal disease, Sinus bradycardia.
4. Should be used with caution in elderly patients undergoing intraurethral instillation as they are tonic-clonic seizures.
5. Caution in patients with spinal deformities, preexisting neurological disease, septicemia and severe hypertension undergoing spinal and caudal-epidural anaesthesia.
6. Preparations containing preservatives should not be used intrathecally and intravascular.

ACETAMINOPHEN

History:

Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced into medical practice under the name of Antifebrin by A. Cahn and P. Hepp in 1886.[29]

But it's unacceptable toxic effects, the most alarming being cyanosis due to methemoglobinemia, prompted the search for less toxic aniline derivatives.



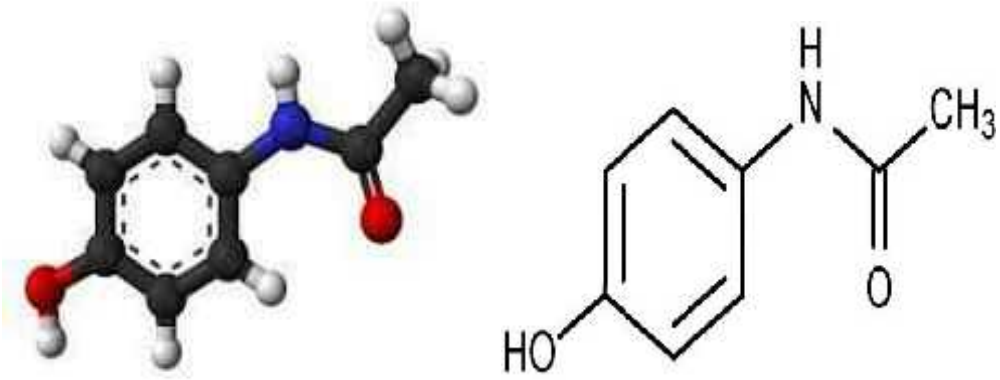
Julius Axelrod (in picture) and Bernard Brodie demonstrated that acetanilide and phenacetin are both metabolized to acetaminophen, which is a better tolerated analgesic.[30]

Acetaminophen was first marketed in the United States in 1953 by Sterling-Winthrop Co., which promoted it as preferable to aspirin since it was safe to take for children and people with ulcers.[31] In 1963, acetaminophen was added to the British Pharmacopoeia, and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents.[32] Concerns about

acetaminophen's safety delayed its widespread acceptance until the 1970s, but in the 1980s acetaminophen sales exceeded those of aspirin in many countries,

Including the United Kingdom. This was accompanied by the commercial demise of phenacetin, blamed as the cause of analgesic nephropathy and hematological toxicity.[33]

Structure



Acetaminophen consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para (1,4) pattern.[31,34] The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen are all conjugated. The presence of two activating groups also makes the benzene ring highly reactive toward electrophilic aromatic substitution. As the substituents are ortho, para-directing and para with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygens and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the phenoxide anion.

Synthesis:

In the laboratory, acetaminophen is easily prepared by nitrating phenol with sodium nitrate, separating the desired para- nitrophenol from the ortho- byproduct, and reducing the nitro group with sodium borohydride. The resultant 4-aminophenol is then acetylated with acetic anhydride. In this reaction, phenol is strongly activating, thus the reaction requires only mild conditions (cf. the nitration of benzene). The industrial process is analogous, but hydrogenation is used instead of the sodium borohydride reduction

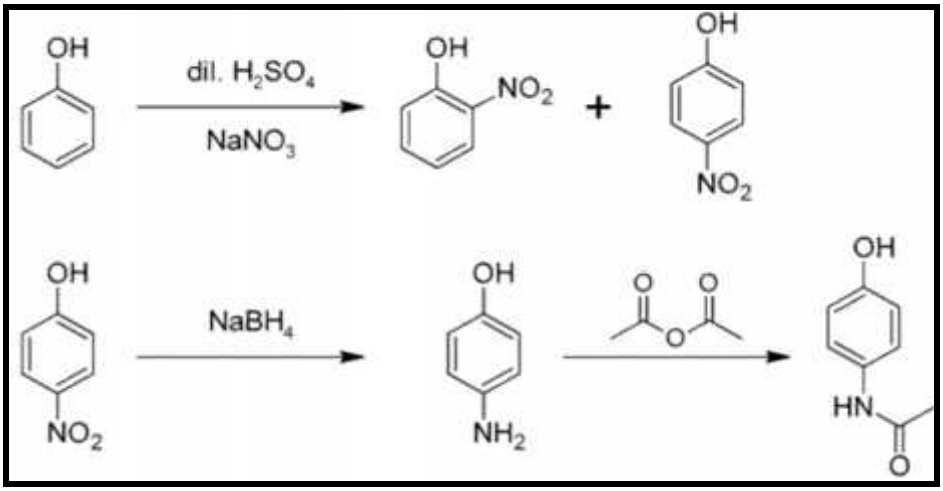


Figure -5. Synthesis of acetaminophen

Classification

Acetaminophen is part of the class of drugs known as "aniline analgesics"; it is the only such drug still in use today. It is not considered an NSAID because it does not exhibit significant anti-inflammatory activity (it is a weak COX inhibitor). This is despite the evidence that acetaminophen and NSAIDs have some similar pharmacological activity.

Available Forms

Acetaminophen is available in a tablet, capsule, liquid suspension, suppository, intravenous, and intramuscular form.Currently, there are two formulations of i.v.acetaminophen: propacetamol, a prodrug of acetaminophen; and the recently approved i.v. acetaminophen. The common adult dose is 500 mg to 1000 mg. The recommended maximum daily dose, for adults, is 4000 mg. In recommended doses, acetaminophen is generally safe for children and infants, as well as for adults, although rare cases of acute liver injury have been linked to amounts lower than 2500 mg per day.

Pharmacokinetics

Intrarvenous acetaminophen escapes first pass metabolism, hence the time course of action is quick with iv acetaminophen as it reaches peak plasma concentration as soon as infusion is complete (about 15 minutes). According to the product information, the analgesic effect starts within 5 minutes, peaks at 1 hour and lasts 4 to 6 hours. This is consistent with a plasma half-life of 2.7 hours - i.e. about two half-lifes. The antipyrexial activity lasts 6 hours.

This time course can be altered. If the speed of infusion is slowed down, then the onset and time to peak effect will be prolonged. If the patient is very heavy or large, the peak effect may be decreased (higher Volume of distribution and hence lower peak plasma levels). In liver failure, the metabolism may reduced, prolonging acetaminophen action. In people taking enzyme-inducing agents or alcohol the metabolism of acetaminophen may increase causing decrease in acetaminophen levels in plasma. Since the elimination is through the kidneys, patients in renal failure may take more time to clear acetaminophen from the body. However, only less than 5% of

given acetaminophen is excreted unchanged, and its metabolites (also excreted through the kidneys) are inactive. Probenecid tends to increase plasma levels of acetaminophen.[35] In the very young, metabolism and elimination take longer.

Metabolism

Main pathways of acetaminophen metabolism. Pathways shown in blue and purple lead to non-toxic metabolites; the pathway in red leads to toxic NAPQI.

Acetaminophen is metabolised primarily in the liver, into non-toxic products.

Three metabolic pathways are notable:

- Glucuronidation is believed to account for 40% to two-thirds of the metabolism of paracetomol.[36]
- Sulfation (sulfate conjugation) may account for 20–40%.[37]
- N-hydroxylation and rearrangement, then GSH conjugation, accounts for less than 15%. The hepatic cytochrome P450 enzyme system metabolizes acetaminophen, forming a minor yet significant alkylating metabolite known as NAPQI (N-acetyl-p-benzo-quinone imine) (also known as acetylimidoquinone) . NAPQI is then irreversibly conjugated with the sulfhydryl groups of glutathione.[38]

All three pathways yield final products that are inactive, non-toxic, and eventually excreted by the kidneys. In the third pathway, however, the intermediate product NAPQI is toxic. NAPQI is primarily responsible for the toxic effects of acetaminophen; this constitutes an example of toxication.

Production of NAPQI is primarily due to two isoenzymes of cytochrome P450: CYP2E1 and CYP1A2. The P450 gene is highly polymorphic, however, and individual differences in acetaminophen toxicity are believed due to a third isoenzyme, CYP2D6. Genetic polymorphisms in CYP2D6 may contribute to significantly different rates of production of NAPQI. Furthermore, individuals can be classified as "extensive", "ultrarapid", and "poor" metabolizers (producers of NAPQI), depending on their levels of CYP2D6 expression. Although CYP2D6 metabolises acetaminophen into NAPQI to a lesser extent than other P450 enzymes, its activity may contribute to acetaminophen toxicity in extensive. At usual doses, NAPQI is quickly detoxified by conjugation with glutathione.[43] Following overdose, and possibly also in extensive and ultrarapid metabolizers, this detoxification pathway becomes saturated, and, as a consequence, NAPQI accumulates causing liver and renal toxicity.

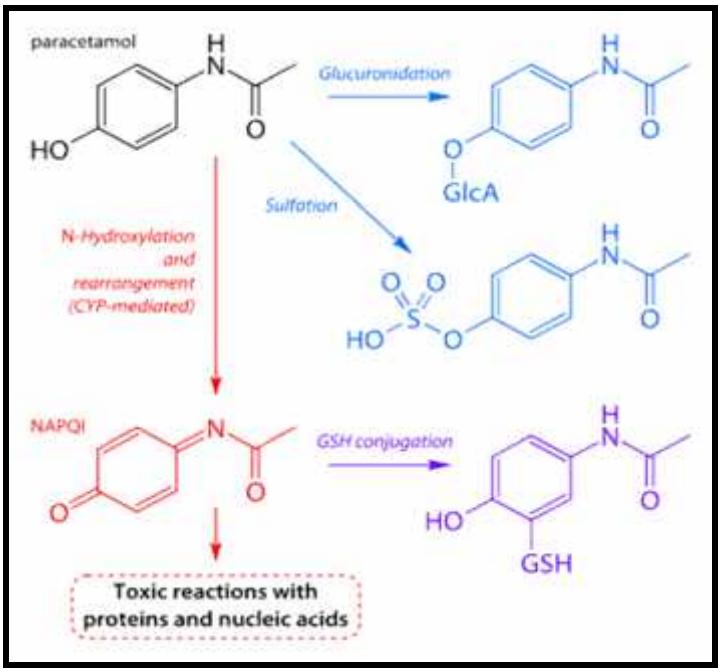


Figure -6. Metabolism of acetaminophen

Mechanism of action:

To date, the mechanism of action of acetaminophen is not completely understood..It has always been thought to have a strong central action, supported by the fact that acetaminophen is found in significant concentrations in the CSF after infusions in adults and in children.[38]

Prostaglandin synthesis relies on the action of cyclooxygenase (COX) enzymes on arachidonic acid. For this to occur, COX must be in an oxidised form. Acetaminophen seems to reduce this oxidised form, rendering the enzyme less effective.[39]

Reduced amount of prostaglandins E2 in the CNS, thus lowering the hypothalamic set-point in the thermoregulatory centre, recent findings suggest that it is highly selective for COX-2, Because of its selectivity for COX-2 it does not significantly inhibit the production of the pro-clotting thromboxanes. The other family of COX enzymes, COX 3, was thought to mediate analgesia in humans[40]but this theory has now lost favour, as COX 3 is not thought to be active in humans.[41]

Acetaminophen is also thought to affect the endogenous cannabinoid system. Acetaminophen is metabolised to AM404, also known as N-arachidonoylphenolamine.[42]

This compound prevents the reuptake of endogenous cannabinoids like anandamide from the synaptic cleft. Since blockade of cannabinoid type 1 receptors attenuate the action of acetaminophen,[43] this theory is gaining credibility. AM404 is also a TPRV1 agonist, which is also activated by the analgesic drug capsaicin. Acetaminophen may act along the same lines.

An article in Nature Communications from researchers in London, UK and Lund, Sweden in November 2011 has found a hint to the analgesic mechanism of acetaminophen and metabolites of acetaminophen e.g. NAPQI, act on TRPA1-receptors in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain.

COX, TPRV1 and cannabinoids in combination could be involved not only in pain, but also also thermoregulatory pathways.[43]

Another receptor for the action of acetaminophen is the 5-HT3 receptor. A 5-HT3 antagonist was found to block the antinociceptive action of intrathecal acetaminophen,[44] supporting this action.

Dosage

Adults: Maximum of 1 gm IM/IV up to 4 times daily.

Children (<33 kg): 15 mg/kg IM / IV up to 4 times daily as required. Minimum interval of 6 hours recommended in-between doses. Maximum dose is 60 mg /kg per day.

Uses:

Acetaminophen is approved for reducing fever in people of all ages. Acetaminophen has a well-established role in pediatric medicine as an effective analgesic and antipyretic.

Acetaminophen is used for the relief of pains associated with many parts of the body. It has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better tolerated than aspirin in patients in whom

excessive gastric acid secretion or prolongation of bleeding time may be a concern.

Acetaminophen can relieve pain in mild arthritis but has no effect on the underlying inflammation, redness, and swelling of the joint. It is as effective as the non-steroidal anti-inflammatory drug ibuprofen in relieving the pain of osteoarthritis of the knee.

Acetaminophen has relatively little anti-inflammatory activity, unlike other common analgesics such as the NSAIDs, aspirin and ibuprofen.

Regarding comparative efficacy, studies show conflicting results when compared to NSAIDs. A randomized controlled trial of chronic pain from osteoarthritis in adults found similar benefit from acetaminophen and ibuprofen.

Indications:

- Acetaminophen is indicated for symptomatic relief of fever
- Temporary reduction of mild to moderate aches and pain associated with cold, flu, headache, muscular aches, sprains, overexertion and osteoarthritis.
- In children, it can be useful for simple pain and discomfort.

Contraindications

- It is not advocated for those allergic to its ingredients.
- Not advocated in severe hepatocellular insufficiency and hepatic failure.
- Acetaminophen injection especially must be advocated with caution in those with a creatinine clearance <30 ml/minute, chronic alcoholism, chronic malnutrition (low reserves of glutathione stores) and dehydration.
- In pregnancy and lactation it should be given only if strictly required.
- There is inadequate safety data for intramuscular (IM) / IV acetaminophen use in neonates, infants and children <6 months of age.

Adverse effects

- In recommended doses, the side effects of acetaminophen are mild to non-existent.
- Skin rashes and other hypersensitivity reactions could occur and rare occasions it may cause hematological changes. Pain at injection site can occur with IM / IV.
- Prolonged daily use increases the risk of upper gastrointestinal complications such as stomach bleeding, and may cause kidney or liver damage.
- Hepatotoxicity, though extremely rare, can occur if therapeutic doses are exceeded. Hepatotoxicity is mediated by a reactive metabolic product (N-acetyl- p-benzoquinone-imine).[31] A conservative estimate of a dose with the potential for hepatotoxicity in an adult is greater than 150 mg/kg body weight.
- A recent review of the tolerability of acetaminophen[35] emphasized that although hepatotoxicity due to acetaminophen over dosage is well recognized, standard recommended doses do not appear to have adverse effects in patients with liver disease. Hence, acetaminophen is not contraindicated in patients with liver disease, provided that recommended doses are not exceeded.[45]

Drug interactions

- Absorption of acetaminophen is increased by concomitant metoclopramide. Probenecid can decrease it's clearance whilst cholestyramine diminishes absorption of acetaminophen when coadministered.

METHODOLOGY

Source of data

Patients between 18 to 60 yrs of either gender, belonging to ASA grade I and II class scheduled for upper limb surgeries at KLES Dr. Prabhaker Kore hospital between Jan 2012 to Dec 2012 were included.

Study design

- A one year randomized control trial.
- Duration of the study(data collection) is for 12 months **.**

Sample size

Total sample size =60 (30 in each group).

Group I	Lignocaine + Normal saline
Group II	Lignocaine +Acetaminophen

Randomization was achieved by computer generated randomization chart.

c) Sample size calculation:

Sample size was calculated using the

Following formula:-

$$n = \frac{2(z\alpha+z\beta)^2 (s_1+s_2)^2}{(\overline{XT} - \overline{X2})2}$$

Level of significance is taken as 5%.

Power of the test used is taken as 80%.

$z\alpha = 1.96 \quad (\alpha = 0.05)$

$z\beta = 0.84 \quad (\beta = 0.2)$

$s1 = 10$

$s2 = 10$

$\underline{x1} = 53$

$\underline{x2} = 38$

With these values, the minimum sample size obtained was 15. For the sake of consistent result 'n' is taken as 30.

e) Selection Criteria:

Inclusion Criteria:

- ASA physical status I and II.
- Age between 18 to 60 years.
- Elective surgeries of upper limb.

Exclusion Criteria:

- Patients with known history of hypersensitivity to any of the drugs used.
- Peripheral vascular disease.
- History of Raynaud's disease, Sickle cell anaemia and Paget's disease.
- Patients with liver diseases
- History of Epilepsy

Methodology:

After obtaining approval of ethical committee and written informed consent for participation in the study, all the 60 patients were randomly allocated into group "I" and group "II" by computer generated randomization method.

Investigations like-

1) Complete blood count

2) Routine urine examination

3) Other investigations like Blood sugar, ECG, Blood urea, Serum creatinine, Liver Function Tests and chest X-Ray were performed.

Two IV cannulae were placed, one in a vein on the dorsum of the operative hand for the IVRA and the second in the opposite hand. After shifting the patient to operation theatre, all the monitors were attached.

Two pneumatic inflatable cuffs, appropriate for limb circumference were applied after proper padding beneath the two cuffs. The arm was exsanguinated by raising the limb above chest for 5 min. After exsanguination of the limb, the proximal tourniquet was inflated to 100mm of Hg above systolic blood pressure. The tourniquet was tested for tightness. The drug solution prepared by third person not involved in the study was injected, as both the patient and monitoring anaesthesiologist were blinded to the drug injected.

Group I -Lignocaine and Normal saline.

GroupII-Lignocaine and Acetaminophen.

In Group 'I' Lignocaine 0.5%(preservative free) was prepared by diluting with normal saline to a volume of 0.5ml/kg(maximum 40 ml)

In Group 'II' Lignocaine 0.5% (preservative free) solution was prepared by diluting with intravenous Acetaminophen(10mg/ml) to a volume of 0.5ml/kg(maximum 40 ml) .

As per randomization, patients were given drug solution which was injected slowly over two minutes and then IV cannula on operative side was removed.

The onset time for sensory blockade is defined as the time elapsed from injection of the drug to a complete sensory block was achieved in all dermatomes

Sensory block was assessed every 30 sec after injection of prepared Lignocaine solution using standardised pinprick technique with a 22G short bevelled needle . The patient's response was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous ulnar, median and radial nerves.

Tourniquet pain was assessed using a visual analogue scale(VAS) with 0=no pain and 10=worst pain imaginable. The time of onset of tourniquet pain i.e. VAS >4 was noted.

Distal cuff was inflated only after patient complained of tourniquet pain and the time of onset of tourniquet pain was recorded. Throughout the procedure standard monitoring was done.

Maximum tourniquet time allowed was 90 minutes. Tourniquet was not deflated even if the procedure was over within 30 minutes.

Any associated complications like perioral numbness, giddiness, tinnitus, nausea, vomiting, pain, skin rashes, hypotension, bradycardia, convulsions and cardiac asystole were noted.

Parameter's Assessed

- Time of onset of sensory block.
- Time of onset of tourniquet pain.

Statistical analysis

Numerical variables like age, weight, duration of surgery, duration of tourniquet pain, onset of tourniquet pain and onset of sensory block were summarized by mean and standard deviation for the two groups and they were compared by using Unpaired't' test.

Gender distribution between two groups was compared by using chi square test.

Significance level was kept at 0.05.

RESULTS

Table -1:-Age distribution

AGE IN YEARS	GROUP I	GROUP II
20-29	11	13
30-39	01	04
40-49	07	04
>50	11	09
MEAN±S.D	39.6±15.35	36.7±14.36

Majority of study subjects were in age group of 20-29yrs. The mean age of patients in group I was 39.6yrs and in group II was 36.7yrs.

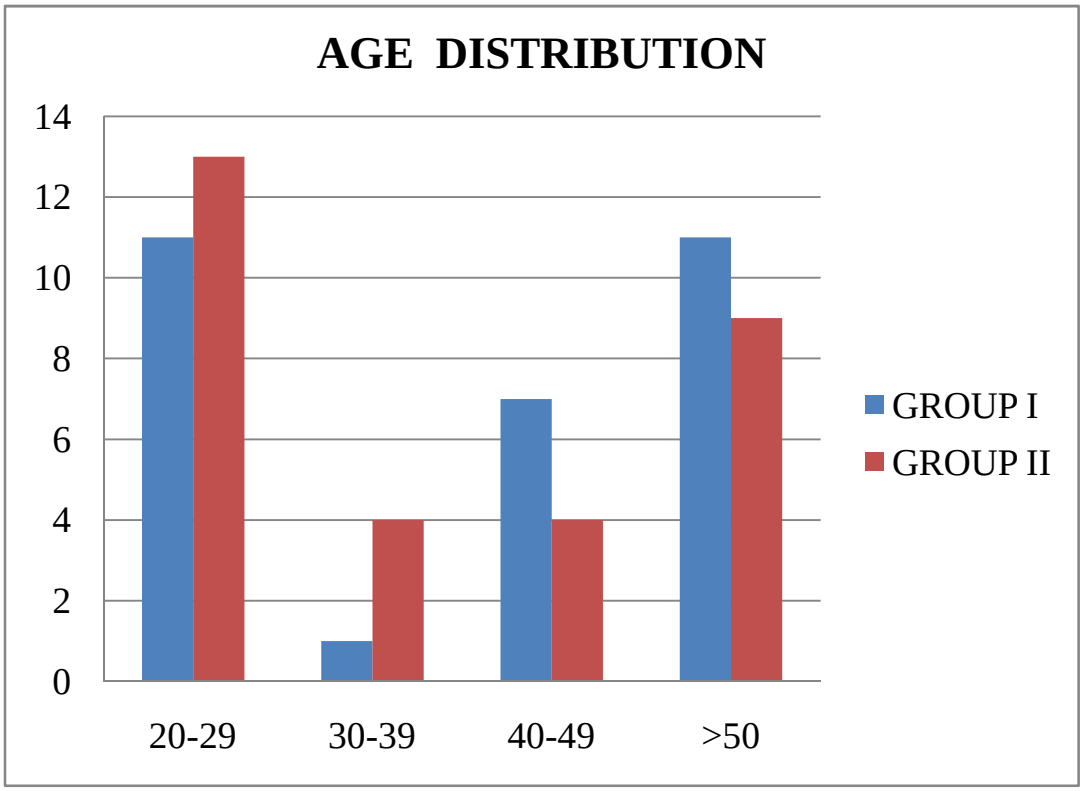


TABLE-2:-Weight distribution

Weight in Kgs	GROUP I	GROUP II
31 – 40	0	0
41 – 50	03	02
51 – 60	06	10
>61	21	18
MEAN±S.D	68.9 ± 12	66.4 ± 10.40

Mean weight of patients in group I was 68.94kgs and in group II was 66.4 kgs.

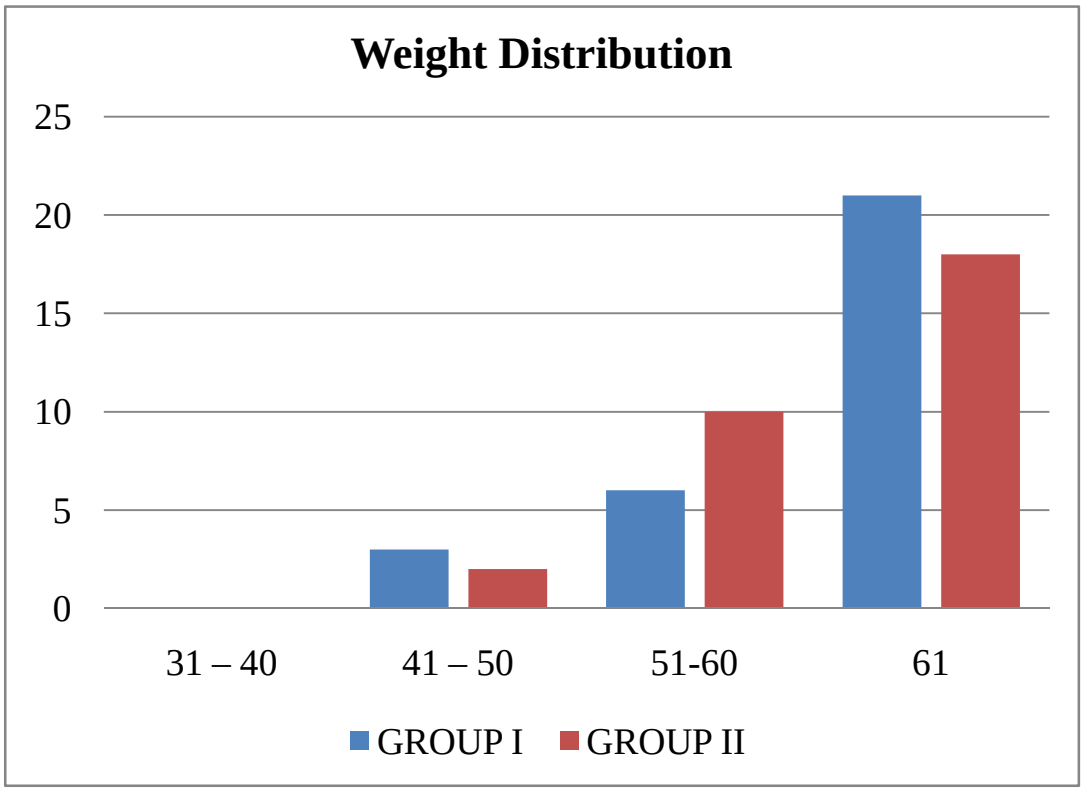


TABLE-3:-SEX DISTRIBUTION

Sex	GROUP I	GROUP II
Male	22	23
Females	08	07
Total	30	30

Males among patients in group I were 22 and females were 08 and among patients in group II males were 23 and females were 07.

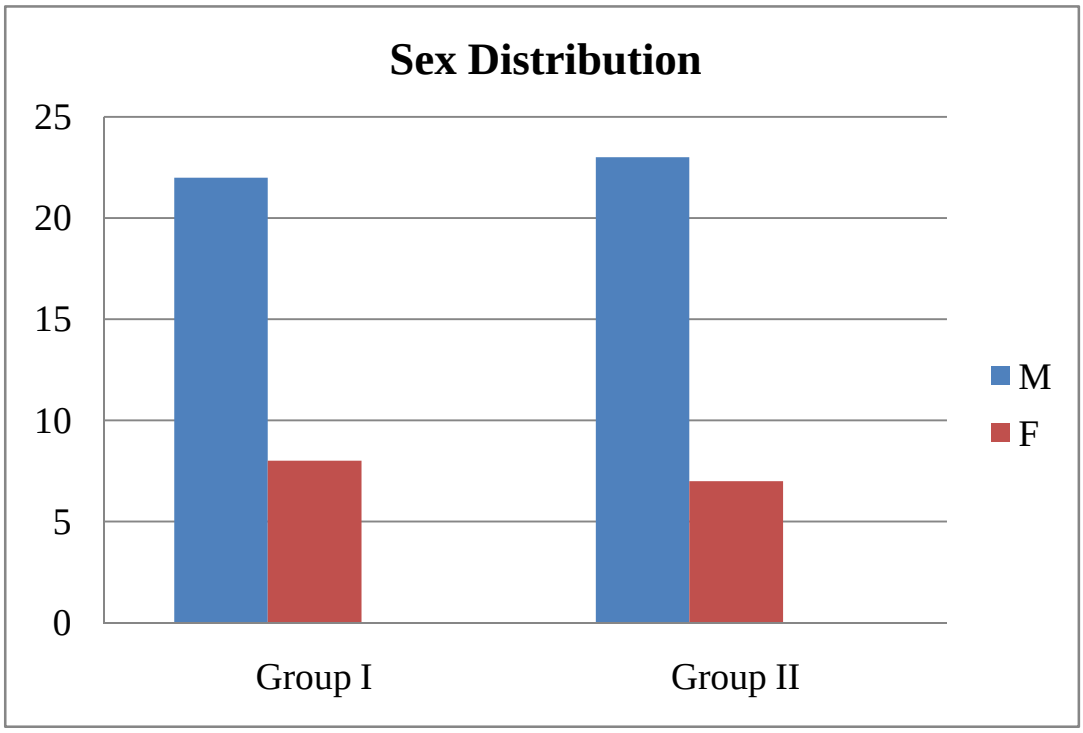


TABLE-4:- DURATON OF SURGERY.

TIME IN MINS	GROUP I	GROUP II
<45	13	07
46—50	02	03
51—55	07	05
56—60	07	14
61—65	01	01
MEAN	48.9±9.74	52.3±8.74

Mean dration of surgery in group I was 48.9 and in group II was 52.34.

TABLE-5. VARIOUS SURGICAL PROCEDURES.

TYPE O SURGERY	GROUP I	GROUP II
BBF FOREARM	00	01
CAR.TUNNEL RELEASE	01	02
CRIF	00	01
EXCI.GANGLION	02	01
INTERNAL FIXATION	14	19
K-WIRE FIXATION	02	01
AMPUTATION OF FINGER	01	00
CONTRACTURE RELEASE	01	00
DEBRIDEMENT	01	00
EXTERNAL FIXATION	02	00
K-WRE REMOVAL	01	00
MASS REXICISION	01	00
PINING	01	00
PLATE REMOVAL	01	00
SUTURING	01	00
THUMB AMPUTATION	01	00
TOTAL	30	30

TABLE-7 COMPARISION OF MEANS AMONG PATIENTS IN GROUP I AND GROUP II.

	GROUP I		**GROUP II**		**P-VALUE**	**SIGNIFICANCE**
	MEAN	S.D	MEAN	S.D		
WEIGHT	68.9	12	66.4	10.40	0.392(>0.05)	NOT SIGNIICANT
AGE	39.6	15.35	36.7	14.36	0.458(>0.05)	NOT SIGNIFICANT
DURATION OF SURGERY	48.9	9.74	52.3	8.74	0.16(>0.05)	NOT SIGNICANT
ONSET OF SENSORY BLOCK	4.6	0.7	1.9	0.61	0.001^{+}(<0.05)	SIGNIFICANT
DURATION OF ONSET OF TOURNIQUET PAIN	26.3	1.60	27.8	2.49	0.009^{+}(<0.05)	SIGNIFICANT

Mean weight in group I was 68.9 and in group II was 66.4, Mean age in group I was 39.6 and in group II was 36.7 and mean duration of surgery in group I was 48.9 and in group II was 52.3.Therefore both the groups were comparable with respect to weight , age and duration of surgery.

Time of onset of sensory block in group I was 4.6 and in group II was 1.9.

Duration of onset of tourniquet pain in group I was 26.3 and in group II was 27.8.

DISCUSSISON

Intravenous regional anaesthesia is a safe, simple to administer and effective method for providing anaesthesia for surgeries on the extremities. It is ideal for short procedures performed on upper limbs.[2]

Preservative free Lignocaine is amide local anaesthetic and considered to be least toxic for use in IVRA. Dosage of 1-2mgkg^{-1} is used for treating ventricular arrhythmias or attenuating the cardiovascular response to endotracheal intubation. In IVRA with conventionally placed tourniquet over the upper arm a relatively large doses of 5 mgkg^{-1} is required to ensure adequate analgesia.[3]

But limitations to its use are slow onset , tourniquet pain and inability to provide postoperative analgesia.

In an attempt to overcome limitations various additives have been administered concomitantly with local anaesthetics[4]. The search continues for an ideal agent, which is devoid of side effects that can be added to local anaesthetics in intravenous regional anaesthesia.

This study was done to evaluate the effect on onset of sensory blockade and tourniquet pain when Acetaminophen was added to Lignocaine for intravenous regional anesthesia (IVRA) in the following groups.

Group I	**Lignocaine + Normal saline**
Group II	**Lignocaine +Acetaminophen**

In the present study, we observed that:-

Onset of sensory block was early among group II(1.9±0.61mins) compared to group I (4.6±0.70mins).

Onset of tourniquet pain was slightly delayed among group II(27.8±2.49mins) compared to group I (26.3±1.60mins), which is statistically significant but clinically not significant.

The observed beneficial effect of Acetaminophen in IVRA on onset of sensory blockade is supported by various studies.

Study done by Celik et al where he has taken ninety patients undergoing elective hand surgery and randanized patients into three groups. 1) Control group receiving 20ml IV 0.9% saline (NS) and NS added to the IVRA solution, 2)group P-IVRA, receiving 20ml 0.9% saline and 20 ml paracetomol added to the IVRA solution,3)group P-IV, receiving 20 ml(200mg) paracetomol IV and NS added to the IVRA solution.

They found that sensory and motor block onset and recovery times were similar between all groups, VAS scores of tourniquet pain were lower at 30 min after tourniquet inflation and at 1, 2, 4, 6 and 24h after tourniquet deflation. Intraoperative Morphine usage was 0.93±1.59 in P-IVRA compared to 1.87±2 in C-IVRA and 2±0.9 in P-IV. Paracetomol consumption was significantly less in group P-IVRA (1.60±1) when compared with group C-IVRA and P-IV i.e. 2.45±0.9 ($p<0.05$).

Acetaminophen is widely used for the pain management and antipyretic as an alternative to Aspirin. Simmons et al. demonstrated a COX-2 variant which is especially sensitive to Paracetomol.It has also been suggested that a spice variant of

COX -1, named COX-3 is related to the mechanism of action of Paracetomol; however , its low expression level, based on genomic and kinetic analysis indicates that this selective interaction is unlikely to be clinically relevant. It suppresses the release of PGE_2 without affecting TXB_2 release or Thrombaxane A synthase expression. Its analgesic effect is attributed to decreased peripheral PGE_2 release in addition to the centrally mediated analgesic effects and activation of descending serotonergic pathways.

Canbay et al. reported that Paracetomol pretreatment appears to be effective in reducing the pain experienced during the IV injection of Propofol. This kind of analgesic effect may be related to preventing the conduction of C fibers, which are more resistant to Lidocaine than A-delta fibers and to the opening of K^+ channels located in the primary afferent nerve endings.[5]

Similar study done by Sen et al to see the analgesic effect of Acetaminophen when added to Lignocaine for intravenous regional anaesthesia and he had taken three groups. In Group 1 IVRA was achieved with 3mg/kg of Lidoocaine diluted with saline to a total of 40ml, 3mg/kg of Lidocaine +300mg of Acetaminophen diluted with saline to a total of 40ml in group 2 and in group 3, 3mg/kg of Lidocaine diluted with saline to a total of 40ml with 300mg of acetaminophen IV immediately after injection of IVRA medication.

He found that mean time to sensory block onset time was 7±3min, 5±2min and 6±3min respectively and there was no significant difference in the onset of sensory block among the groups ($p>0.05$). In this study they have not evaluated for the onset of tourniquet pain.[20]

In our study we compared two groups, groupI -Lignocaine with normal saline and group II-lignocaine with paracetomol and we found that mean time for the sensory block onset time was 4.6±0.70 in group I and 1.9±0.61 in group II which is statistically significant ($p<0.01$) and shows that the onset of sensory block was early among group II compared to group I,which is clinically significant and the time of onset of tourniquet pain in group I was 26.3±1.60 and in group II was 27.8±2.49 which is statistically significant but clinically not significant.

These results are in contrast to the above two study results where they found no difference in the onset of sensory blockade among the study groups.

Another study by Alireza Mirkheshti, Mohammad Reza Aryani, Poujia Shojaei, and Ali Dabbagh was done to compare the analgesic effects of “magnesium with lidocaine”, “acetaminophen with lidocaine”, and “placebo plus lidocaine” on block characteristics for intravenous regional anesthesia (IVRA) in patients undergoing upper extremity orthopaedic surgery. In the first group, IVRA using Lidocaine and Magnesium(3 mg/kg of Lidocaine plus 1 g of Magnesium sulphate i.e. 5 ml of 20% solution), in the second group, IVRA using Lidocaine and Acetaminophen (3 mg/kg of Lidocaine plus 300 mg of Acetaminophen) and in the third group, IVRA using Lidocaine and placebo. In the three groups the drug combination was increased to 50 ml using normal saline.

Regarding the times for sensory block, the time from drug injection to sensory block onset was shortest in the magnesium plus lidocaine group (the first group), while there was no difference regarding the duration of sensory block between the three groups.

Regarding the times for motor block, the time from drug injection to the time of motor block onset was the shortest in the first group (lidocaine plus magnesium), while there was no statistically significant difference between the second (acetaminophen plus magnesium) and third (placebo plus lidocaine) groups. Also, regarding the duration of the motor block, it was the longest in the first group, while there was no difference between the second and the third group.

The values related to the pH before the block were same between the three groups while the pH after the block was significantly higher in the second group, while there was no difference between the first and the third groups.

There was no statistically significant difference between the three groups regarding these variables: partial venous pressure of oxygen before the block; partial venous pressure of carbon dioxide before the block; partial venous pressure of oxygen after the block; partial venous pressure of carbon dioxide after the block.[21]

But in our study when we campared group I i.e Lignocaine with normal saline and group II i.e. Lignocaine with Paracetomol , we found that there is early onset of sensory block in group II (1.9±0.61) compared to group I(4.6±0.70) but there is no clinically significant results in the onset of tourniquet pain between two groups.

Another study done by Ko, et al to compare the effects of Acetaminophen to Ketorolac when added to Lidocaine for intravenous regional anesthesia. They have taken sixty patients undergoing hand or forearm surgery under IVRA and were assigned to three groups: Group C received 0.5% lidocaine diluted with 0.9% normal saline to a total volume of 40 ml (n = 20), Group P received 0.5% lidocaine diluted with intravenous Acetaminophen 300 mg to a total volume of 40 ml (n = 20) and

Group K received 0.5% lidocaine diluted with 0.9% normal saline plus Ketorolac 10 mg made up to a total volume of 40 ml (n = 20).

They found Sensory block onset time was significantly shorter in Group P (2.3±1.4) than in group C (3.6±1.6) $P < 0.05$. There was no significant difference among groups when compared for sensory block recovery time. Tourniquet pain onset time was significantly longer in Group P (34.6±7.8) than other groups ($P < 0.05$). There was no significance among groups for intraoperative total amount of fentanyl consumption ($P = 0.093$).

This study concluded that the addition of intravenous Acetaminophen to Lidocaine in IVRA significantly shortens the onset time of sensory block, but not intravenous Ketorolac. The addition of both drugs may not affect intraoperative analgesia and tourniquet pain. However, both drugs would improve postoperative analgesia in postanesthesia care unit.[22]

In above mentioned studies they have taken constant amount of Acetaminophen i.e 300mg but in our study we have taken Acetaminophen in proportionate to body weight along with Lignocaine i.e 5mg/kg. Sensory block onset time in group II was 1.99±0.61 and in groupI was 4.55±0.69 and these results are almost similar to the above study results. Tourniquet pain onset time in group II was

27.82±2.5 and in group I was 26.35±1.6 which is clinically insignificant. In our study we have not seen for postoperative analgesia and amount of analgesic consumption.

Future scope

Further research needs to be done to establish the appropriate dosage of acetaminophen in IVRA.

LIMITATIONS

We have measured only the onset of sensory block and onset of tourniquet pain and we did not look for sensory block and motor block recovery time, postoperavive analgesia and amount of analgesic requirement postoperatively.

One more limitation of our study is nonstandardisation of PH of both the solutions in the study since pH of local anesthetics affects the nerve penetration and in turn affects onset of sensory blockade.

CONCLUSION

This study concludes that addition of Acetaminophen to Lignocaine in Intravenous Regional anaesthesia (IVRA) significantly shortens the onset time of sensory block.

SUMMARY

The aim of the study was to compare the analgesic efficacy of Lignocaine alone versus combination of Lignocaine with a Acetaminophen when used in IVRA with respect to onset of sensory block and tourniquet time.

We observed that the mean time for the onset of sensory block in group II was 1.9±0.61min and in group I was 4.6±0.70min which is clinically significant and Tourniquet pain onset time in group II was 27.8±2.49 min and in group I was 26.3±1.60 which is statistically significant but clinically not significant.

Based on results obtained from our study we conclude that, addition of Acetaminophen to Lignocaine in IVRA significantly shortens the onset time of sensory block but there is no clinically significant difference in the onset of tourniquet pain .

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ANNEXURE-I

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____ we are requesting you to enroll yourself in study titled **",** conducted by **KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELGAUM** conducted by J.N. Medical College, Belgaum under KLE university, Belgaum.

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.MedicalCollege. If you decide to participate you are free to withdraw at any time.

The purpose of research is to know **"Comparison of analgesic effect of Lignocaine and Lignocaine combined with Acetaminophen in Intravenous regional anaesthesia-A one year randomized control trial".**

Procedure Involved :

If you agree to enroll yourself in my study, I will ask your present past and family history. Then you will be clinically examined in detail and routine investigations like Hb, TC ,DC, Platelet Count, RBS, Blood Urea, SerumCreatinine,LFT, Blood Grouping, Chest X-ray, ECG, Urine Examination will be done. Two iv cannulae will be placed, one in the operative hand for IVRA and second in the opposite hand. Two

pneumatic inflatable cuffs are applied to the limb and proximal cuff is inflated. You will be given drug solution(depending on which group you belongs , group 1-Lignocaine and Normal saline and group 2-Lignocaine and Acetaminophen) which will be injected slowly over two minutes and then iv cannula on operative side will be removed.

Risks There is no risk involved by adding acetaminophen IVRA. Rarely it causes allergic skin reactions, however, if there is a pre-existing liver insufficiency, Acetaminophen can be hepatotoxic. Lignocaine can rarely cause perioral numbness, giddiness, tinnitus, nausea, vomiting, pain, skin rashes, hypotension, Bradycardia, convulsions and cardiac asystole.

Benefits: It is an effective and safe anaesthesia for upper limb surgeries with good post-operative pain relief.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E.S hospital.

Alternatives :

Even if you decline the participation in the study, you will get the routine line of management.

Privacy and Confidentiality:

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial Incentives for participation:

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation:

In the event of injury related to the study, treatment will be made available through KLES Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law.

Questions:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Anaesthesiology, KLES Hospital and MRC, Belgaum

CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

I, _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____

Date :

Witness Name : _____ Signature: _____ Date :

Investigators Name: _____Signature: _____ Date :

Place : _____

ANNEXURE -IV

MASTER CHART

ASA-American Society of Anaesthesiologists

CRIF-Closed Reduction and Internal Fixation

ANNEXURE-II

PROFORMA

"COMPARISON OF ANALGESIC EFFECT OF LIGNOCAINE AND LIGNOCAINE COMBINED WITH ACETAMINOPHEN IN INTRAVENOUS REGIONAL ANAESTHESIA-A ONE YEAR RANDOMIZED CONTROL TRIAL"

Name & Address of the patient : _____

_____

Age of the Patient:_____ IP. No. _____

Weight of Patient:_____ ***Random No._____***

Anaesthesiologist : _____ ***Surgeon : _____***

PREANAESTHETIC EVALUATION :

Chief Complaints:

Past History:

1. History of Hypertension, Diabetes Mellitus, G.E reflux, Addiction.
2. History of usage of acetaminophen, opioids, or NSAIDs 48 hrs before surgery.
3. History of renal disease, hepatic disease and neurological diseases.
4. History of allergy to analgesic drugs such as Paracetomal .

Family History

General Physical Examination :

Weight : Temperature : Pallor : Height

Cyanosis : Pedal Edema : Clubbing :

Pulse : B.P : RR :

M.P Grading

Thyro mental distance Mouth opening

TMJ examination

SYSTEMIC EXAMINATION :

Respiratory System :

Cardiovascular System :

Central Nervous system: Per Abdomen :

Spine assessment

INVESTIGATIONS:

Diagnosis :

Proposed Surgery:

e) Selection Criteria:

Inclusion Criteria:

- ASA physical status I and II.
- Age between 18 to 60 years.
- Elective surgeries of upper limb.

Exclusion Criteria:

- Patients with known history of hypersensitivity to any of the drugs used.
- Peripheral vascular disease.
- History of Raynaud's disease, Sickle cell anaemia and Paget's disease.
- Patients with liver diseases.
- History of Epilepsy.

Methodology:

- After obtaining approval of ethical committee and written informed consent for participation in the study, all the 60 patients will be randomly allocated into group "I" and group "II" by computer generated randomization method.

- Investigations like-

  1) complete blood count

  2) Routine urine examination

  3) Other investigations like Blood sugar, ECG, Blood urea, Serum creatinine, Liver Function Tests and chest X-Ray will be performed.

- Two IV cannulae will be placed, one in a vein on the dorsum of the operative hand for the IVRA and the second in the opposite hand. After shifting the patient to operation theatre, all the monitors will be attached.

- Two pneumatic inflatable cuffs, appropriate for limb circumference will be applied after proper padding beneath the two cuffs. The arm will be exsanguinated by raising the limb above chest for 5 min. After exsangulation of the limb, the proximal tourniquet will be inflated to 100mm of Hg above systolic blood pressure. The tourniquet will be tested for tightness. The drug

solution prepared by third person not involved in the study will be injected, as both the patient and monitoring anaesthesiologist will be blinded to the drug injected

Group I -Lignocaine and Normal saline.

Group II- Lignocaine and Acetaminophen.

In Group 'I' Lignocaine 0.5 % (preservative free) was prepared by diluting with normal saline to a volume of 0.5ml/kg(maximum 40 ml)

In Group 'II' Lignocaine 0.5% (preservative free) solution was prepared by diluting with intravenous Acetaminophen(10mg/ml) to a volume of 0.5ml/kg(maximum 40 ml) .

- As per randomization, patients will be given drug solution which will be injected slowly over two minutes and then IV cannula on operative side will be removed.

- The onset time for sensory blockade is defined as the time elapsed from injection of the drug to a complete sensory block was achieved in all dermatomes
- Sensory block was assessed every 30 sec after injection of prepared Lignocaine solution using standardised pinprick technique with a 22G short bevelled needle . The patient's response was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous ulnar, median and radial nerves.
- Tourniquet pain will be assessed using a visual analogue scale(VAS) with 0=no pain and 10=worst pain imaginable. The time of onset of tourniquet pain i.e. VAS >4 will be noted.

- Distal cuff will be inflated only after patient complaints of tourniquet pain and the time of onset of tourniquet pain will be recorded. Throughout the procedure standard monitoring will be done.

- Maximum tourniquet time allowed will be 90 minutes. Tourniquet will not be deflated even if the procedure is over within 30 minutes.

- Any associated complications like perioral numbness, giddiness, tinnitus, nausea, vomiting, and pain, skin rashes, hypotension, bradycardia, convulsions and cardiac asystole will be noted.

Assessment of time of onset tourniquet pain and sensory block:-

	Group I	**Group II**
Onset time of tourniquet pain.		
Onset time of sensory block.		

ANALYSIS PLAN

"Comparison of analgesic effect of Lignocaine and Lignocaine combined with Acetaminophen in Intravenous regional anaesthesia-A one year randomized control trial".

DR ARCHANA G V

Post Graduate Student,

Department of Anaesthesiology,

J. N. Medical College,

K.L.E. University, Belgaum 10.

Chi square will be used to compare both groups, A p-value < 0.05 will be accepted as statistically significant.

Assessment of time of onset tourniquet pain and sensory block will be compared in 2 groups:-

	Group I	**Group II**
Onset time of sensory block.		
Onset time of tourniquet pain.		

Demographic data will be comparable between the 2 groups:

Group	**Group I**	**Group II**
Age		
Sex		
ASA (1 / 2)		
Weight		

ANNEXURE-III

PHOTOGRAPHS

1.Tourniquet **2. Eschmark bandage**

3. IV Acetaminophen **4. 2% Lignocaine (preservative free)**

S.No	IP no	Age	sex	weight	ASA grade	Type o surgery	Duration of surgery	Duration of tourniquet	Onset of sensory block	Onset of tourniquet pain	Complications
1	431678	53	M	66	I	Internal fixation	55	55	4	25	No
2	443105	45	M	70	I	Internal fixation	60	60	4.5	26	No
3	453710	58	M	82	I	Internal fixation	50	50	4.5	26	No
4	454433	59	M	88	I	Internal fixation	55	55	5	25	No
5	455355	18	F	52	I	Internal fixation	45	45	4	25	No
6	458674	25	M	60	I	Plate removal	60	60	4.5	24	No
7	460161	56	F	60	I	suturing	35	35	5.5	28	No
8	462260	18	M	70	I	Mass excision	60	60	5	26	No
9	461796	20	M	64	l	K wire removal	30	30	3.5	24	No
10	462465	45	M	74	l	Thumb amputat-ion	40	40	5	27	No
11	464033	26	M	76	l	Excision of ganglion	44	44	4	24.5	No
12	465362	60	M	56	l	Internal fixation	58	58	3.5	29	No
13	465762	59	M	80	l	Internal fixation	60	60	4	26	No
14	466487	51	F	80	l	Contracture release	36	36	5.5	28.5	No
15	464033	26	M	76	l	Excision of ganglion	45	45	4.5	29	No
16	467090	40	F	76	l	Carpel tunnel release	36	36	5.5	28	No
17	467668	51	F	56	l	Internal fixation	55	55	4	26.5	No
18	468231	53	F	70	l	K –wire fixation	40	40	4	26	No
19	465436	50	M	80	l	Internal fixation	50	50	5	27	No
20	466576	47	M	82	l	Internal fixation	52	52	5	25	No
21	466107	48	F	86	l	External fixation	55	55	4	26.5	No
22	470869	54	M	76	I	pinning	30	30	5	27	No
23	471003	45	M	70	l	K –wire fixation	40	40	6	24	No
24	471518	24	M	56	l	Amputa-tion of finge	44	44	4.5	23	No
25	472853	18	F	50	l	debridement	44	44	5	26	No
26	473053	22	M	64	l	Internal fixation	59	59	4	28	No
27	475946	20	M	46	l	Internal fixation	55	55	3.5	27	No
28	476286	48	M	80	l	External fixation	54	54	3.5	27.5	No
29	476874	18	M	46	l	Internal fixation	60	60	5.5	28	No
30	478208	31	M	76	l	Internal fixation	61	61	5	28	No

S.No	IP no	Age	sex	weight	ASA grade	Type o surgery	Duration of surgery	Duration of tourniquet	Onset of tourniquet pain	Complications
1	432890	42	M	60	I	BB# forearm	55	55	30	No
2	436549	59	M	66	I	CRIF	60	60	29	No
3	441331	32	M	76	I	Internal fixation	50	50	29	No
4	453638	18	M	60	I	Internal fixation	40	40	28.5	No
5	454304	24	M	84	I	Internal fixation	45	45	30	No
6	489988	52	M	72	I	K-Wire fixation	60	60	35	No
7	460587	58	M	70	I	Internal fixation	56	56	28	No
8	460870	59	F	70	I	Internal fixation	40	40	29	No
9	462890	20	F	60	I	Excision of ganglion	42	42	28.5	No
10	432512	52	F	70	l	Carpel tunnel release	30	30	29.5	No
11	464558	56	M	80	l	Internal fixation	55	55	26	No
12	464991	25	M	60	l	Internal fixation	58	58	27	No
13	462110	25	M	60	l	Internal fixation	60	60	29	No
14	466836	59	M	70	l	Internal fixation	56	56	27.5	No
15	467934	25	M	46	l	Internal fixation	55	55	28	No
16	469235	31	M	66	l	Internal fixation	56	56	29	No
17	469192	20	F	50	l	Excision of ganglion	35	35	28	No
18	481196	43	M	72	l	Internal fixation	58	58	29.5	No
19	481743	45	F	70	l	Carpel tunnel release	38	38	29	No
20	485453	26	M	64	l	Internal fixation	60	60	28	No
21	489185	52	F	88	l	Internal fixation	62	62	25	No
22	487571	24	M	86	l	Internal fixation	59	59	20	No
23	479309	55	M	80	l	Internal fixation	55	55	25	No
24	480208	23	M	60	l	Excision of ganglion	59	59	27	N0
25	482704	26	M	56	l	Excision of ganglion	57	57	29	No
26	482341	23	M	60	l	Internal fixation	55	55	27	No
27	482023	26	F	62	l	Internal fixation	60	60	26	No
28	406582	40	M	66	l	Internal fixation	59	59	26	No
29	484236	32	M	54	l	Excision of ganglion	46	46	24	No
30	486231	30	M	55	l	Excision of ganglion	48	48	28	No