/“A COMPARATIVE STUDY OF BUTORPHANOL V/S BUPRENORPHINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK FOR POSTOPERATIVE ANALGESIA”

Submitted by

DR. VINOD.CN

Dissertation submitted to the

RAJIV GANDHI UNIVERSITY OF HEALTH SCIENCES, KARNATAKA, BANGALORE

In partial fulfillment of the requirements for the degree of

MD

In

ANAESTHESIOLOGY

Under the guidance of

DR. D.G.TALIKOTI$_{\text{M.D.,D.A,}}$
PROFESSOR & HEAD
DEPARTMENT OF ANAESTHESIOLOGY

B. L. D. E. A’S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, BIJAPUR.

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RAJIV GANDHI UNIVERSITY OF HEALTH SCIENCES
KARNATAKA, BANGALORE.

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I hereby declare that this dissertation entitled **"A COMPARATIVE STUDY OF BUTORPHANOL V/S BUPRENORPHINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK FOR POSTOPERATIVE ANALGESIA"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. D.G.TALIKOTI** **M.D.,D.A.** Professor & Head, Department of Anaesthesiology

Date:

Place: Bijapur **DR.VINOD.CN**

B. L. D. E. A'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, BIJAPUR.

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Date:

Place: Bijapur

DR. D.G.TALIKOT$_{\text{M.D.,D.A,}}$
PROFESSOR & HEAD
DEPARTMENT OF ANAESTHESIOLOGY

B. L. D. E. A'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, BIJAPUR.

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DR. D.G.TALIKOTI M.D.,D.A,

PROFESSOR & HEAD
DEPARTMENT OF ANAESTHESIOLOGY
B.L.D.E.A's SHRI. B. M. PATIL
MEDICAL COLLEGE, HOSPITAL
AND RESEARCH CENTRE, BIJAPUR

Date:

Place: Bijapur.

B. L. D. E. A'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, BIJAPUR.

ENDORSEMENT BY THE PRINCIPAL

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DR. M.S.BIRADAR MD
INCHARGE PRINCIPAL
BLDEA's SHRI. B. M. PATIL
MEDICAL COLLEGE, HOSPITAL
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Date:

Place: Bijapur

Dr. VINOD.CN

LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
BP	Blood Pressure
PR	Pulse Rate
cms	Centimeters
GABA	Gamma Amino Butyric Acid
IM	Intramuscular
IV	Intravascular
kg	Kilogram
L.A.	Local Anaesthetic
min	Minutes
mg	Milligram
ml	Milliliter
mm	Millimeter
NIBP	Non Invasive Blood Pressure
NSAIDS	Non Steroidal Anti Inflammatory Drugs
PAG	Periaqueductal Gyrus
PONV	Post Operative Nausea & Vomiting
VAS	Visual Analogue Scale
yrs	Years

ABSTRACT

INTRODUCTION:

Supraclavicular Brachial plexus block provides anaesthesia for surgeries around elbow, forearm and hand. With advent of opioid receptors, variety of opioid agents are used for postoperative analgesia via brachial plexus block. Butorphanol and Buprenorphine can be used along with local anaesthetics to provide post op analgesia.

AIMS:

1) To study the onset and extent of blockade.

2) To study and compare perioperative complications.

3) To compare the duration of postoperative analgesia in two groups.

METHODOLOGY:

A study was carried out in 30 patients aged 18-60yr of ASA grade I&II of either sex in each group undergoing orthopedic upper limb surgeries via supraclavicular brachial plexus block. Injection Butorphanol 1mg (Group-I)and Buprenorphine100µg (Group-II) were added to local anaesthetic mixture. Study was carried out at Shri B.M.Patil medical College& Hospital, Bijapur between the academic years 2007 to 2009 after taken informed consent under medical ethics. All patients were observed for onset of sensory and motor blockade, extent of blockade & Complications. PR, BP were monitored intraoperatively every 15 min of interval and postoperatively. All patients were observed for analgesia hourly until patient demanded analgesia post-operatively by VAS pain score.

SUMMARY OF RESULTS:

Duration of sensory as well as motor and also complete blockade were comparable in both Groups which shows that Group II Buprenorphine had delayed onset compared to Group I Butorphanol. In Group I patients, VAS score was 39.44 ± 16.66 at the end of 5 hours while in Group II patients 50.35 ± 25.65 VAS score at the end of 8 hours. So the duration of analgesia was upto 5-6 hours in Group I, where it was upto 8-9 hours in Group II.

CONCLUSION:

Both drugs are potent analgesic in brachial plexus block, but Buprenorphine is more potent and produces longer duration of postoperative analgesia than Butorphanol.

KEY WORDS :

Butorphanol, Buprenorphine, Supraclavicular Brachial Plexus Block, Postoperative Analgesia

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INTRODUCTION

"For all the happiness, mankind can gain is not in pleasure,

but in rest from pain"-John Dryden (1631 – 1701)

Effective pain control is essential for optimal care of surgical patients, especially in patients undergoing orthopedic surgeries as these patients suffer from considerable pain in the postoperative period.

Acute postoperative pain is a complex physiological reaction to tissue injury or disease. Its manifestation of autonomic, psychological and behavioral responses results in unpleasant, unwanted sensory and emotional experience. Despite advances in knowledge of patho-physiology of pain, pharmacology of analgesics and development of effective techniques for post-operative pain control, many patients continue to experience considerable discomfort.[1, 2]

Brachial Plexus block provides adequate anaesthesia and post operative analgesia for all the upper limb procedure. Supraclavicular brachial plexus block provides anaesthesia for surgeries around elbow, forearm and hand. With this technique, land marks are easy to locate and tourniquet pain is better tolerated.

With advent of opioid receptors, variety of opioid agents are used for post operative analgesia via brachial plexus block. Butorphanol, a synthetic opioid is seven times more potent than morphine. Buprenorphine, a semisynthetic thebaine derivative is more potent than morphine, pethidine, pentozocine and the duration of analgesia is longer than all.

Combination of two local anaesthetics e.g. short acting lignocaine and long acting bupivacaine has been used to speed up the onset and prolong the anaesthesia.Buprenorphine added to the local anaesthetic solution for axillary or supraclavicular brachial plexus block prolongs post operative analgesia as do the butorphanol ,tramadol,clonidine etc.[3]

The present study is conducted to assess the safety and efficacy of post operative analgesia between butorphanol and Buprenorphine administered through Supraclavicular brachial plexus block.

AIMS OF STUDY

1. To assess and compare the safety and efficacy of postoperative analgesia between butorphanol and buprenorphine administered through supraclavicular brachial plexus block in patients undergoing orthopaedic upper limb surgeries.

2. To compare the degree and duration of analgesia,cardio respiratory effects and side effects between butorphanol and buprenorphine.

REVIEW OF LITERATURE

Pain is one of the most important concern of mankind and one of the foremost factor that has influenced the course of history. No one can share the gravity and severity of other's pain. Persistent pain is the most frequent cause of disability and it constitutes a major national world health economic problem.

Since 1880, concept of regional analgesia existed and propagated by various workers. In recent years it has gained momentum and now a days role of regional analgesia for postoperative pain relief is a current tradition. With advent of opioid receptors, variety of opioid agents are used for this purpose.

In 1884, Halsted[4] performed the first brachial plexus nerve block when he found the cords and nerves of the brachial plexus, after blocking the roots in the neck with cocaine solution.Hirschel and Kulemkonepff working independently, were the first to inject the brachial plexus percutaneously (Blindly through the skin) without exposure of nerves.

In 1964, Alon P. Winnie and Vincent J. Collins[5] described the subclavian perivascular technique by applying concept of continuous facial sheath around brachial plexus nerves from the transverse process to several centimeter beyond the axilla.

Controlled studies were carried out on Butorphanol by Dobkin[6] and Lippmann et al.[7] They compared analgesic efficacy of Butorphanol with Morphine and showed that Butorphanol was seven times more potent than Morphine on a weight for weight basis. In these studies, side effects were minimal. Neither Butorphanol nor Morphine produced any hemodynamic changes.

In 1983, Egon Lanz, Dieter Theiss and Danilo Jankovic[8] described extent of blockade following various techniques of brachial plexus block. The difference in extent of blockade resulting from use of four different techniques suggest that the choice of technique should be determined by sites of operation as follows.The supraclavicular technique is dense for surgery of upper arm, elbow and forearm, while interscalene is better for surgery of clavicle, shoulder and upper arm, and axillary is better for forearm and hand surgery.

In 1984, Yung-fong and Micheal S. Weinstem[9] compared Butorphanol and Morphine in Balanced anaesthesia and found that Butorphanol (0.06-0.1 mg/kg) has an analgesic action similar to that of Morphine (0.3-0.5 mg/kg). Patients in Butorphanol group had less respiratory depression as determined by PaCO2 value in the recovery room, less nausea and less vomiting than those given Morphine. Neither group had hallucination nor dysphoria.

In 1989, Viel EJ, Eledjam JJ, De La Coussaye JE, D'Athis F[10] conducted comparison study for post operative pain relief in brachial plexus block with Buprenorphine and Morphine. After operating, using three point pain scale, quality of analgesia was evaluated every hour for six hours then every two hours for next six hours and then at 12, 24, 36 and 48 hours. A significant difference in quality of analgesia was found and was consistently superior with Buprenorphine. The duration of analgesia was nearly thrice with Buprenorphine group. They concluded that Buprenorphine injection into brachial plexus sheath is an efficient way to assure control of post operative pain after upper limb surgery.

In 1995, Z. Wajima, Y. Nakajima and C. Kim[11] conducted study on continuous intravenous Butorphanol compared with Brachial plexus infusion of Butorphanol for post operative analgesia after operations on the upper extremities.

After operation VAS score at 6 hr did not differ in the two groups while at 9 hr it was significantly higher in the IV group as compare to brachial plexus group. So they concluded that Butorphanol via brachial plexus block produces significant prolonged duration of analgesia as compared to intravenous Butorphanol. In the study, respiratory depression was not observed, incidence of nausea and vomiting were same in both the groups.

In 1995, Z. Wajima, T. Shitara, Y. Nakajima, C. Kim[12], have studied comparison of continuous brachial plexus infusion of Butorphanol 2 mg (Group-B), Mepivacaine 0.5% (Group-M) and Mepivacaine Butorphanol (Group-MB) with the volume of 50 ml in each solution, administered at a rate of 50 ml per 24 hrs. At 3 hr after operation, VAS score was significantly higher in group M and in group-B than in group MB. There was a significant difference in the incidence of nausea in Group-B as compared with Group-M. So they have reported that addition of Butorphanol to Mepivacaine prolongs post operative analgesia.

In 1997, Z. Wajima et al[13] conducted study on continuous brachial plexus infusion of mixture of M epivacaine 0.5% and Butorphanol 6 mg at rate of 144ml/72 hrs into two groups with initial bolus dose of Butorphanol (1 mg) and Mepivacaine 1.5% (10 ml) in Group-B. After operation VAS score did not differ between the two groups as well as no significant difference was noted in the incidence of side effects between the two groups. They concluded that continuous Butorphanol 2 mg per day with 0.5% Mepivacaine provided sufficient post operative analgesia after upper limb surgery.

In 1997, Bazin JE et al[14] Conducted study on comparison of the duration of analgesia produced by a mixture of Lignocaine and Bupivacaine either alone or combined with Morphine (75 μg/kg), Buprenorphine (3 μg/kg) or Sufentanil (0.3

μg/kg) in 80 patients after brachial plexus block for orthopaedic surgery of the upper limb. The characteristics of analgesia were evaluated hourly using a visual analogue scale. They concluded that the addition of an opioid to a local anaesthetic mixture lengthens the duration of analgesia.

In 2001, Candido KD et al[15] conducted comparision study of Buprenorphine with Local anaesthetics in one group and Local anaesthetics alone in other group in subclavian perivascular brachial plexus block. The result was the mean duration of post operative pain relief following the injection of Local anaesthetic alone was 5.3 hrs as compared with 17.4 hrs when Buprenorphine was added. They concluded that the addition of Buprenorphine to the Local anaesthetics used for brachial plexus block provides a 3 fold increase in the duration of post operative analgesia.

In 2002, Salins SR, Abraham V, Kaur B, Abraham-I[16] conducted study on extension of brachial plexus block with 1.5% Lignocaine Adrenaline and Buprenorphine a comparison with 1.5% Lignocaine and Adrenaline. Although the addition of Buprenorphine had no significant effect on the quality of analgesia but the duration of analgesia was significantly prolonged more than three times than other group.Therefore they concluded that the addition of Buprenorphine is a suitable drug for prolonging the duration of analgesia when added to 1.5% Lignocaine and Adrenaline when given for brachial plexus block.

In 2007,Jigna Shah,Vandana Trivedi[17] conducted comparative study of Inj.Butorphanol v/s Inj.Buprenorphine in Brachial Plexus block via supraclavicular approach for post operative analgesia. The characteristics of analgesia were evaluated hourly using a visual analogue scale. They concluded that the duration of post operative analgesia was longer in buprenorphine group.No other side effect was seen apart from vomiting in both groups.

ANATOMY OF BRACHIAL PLEXUS[18,19]

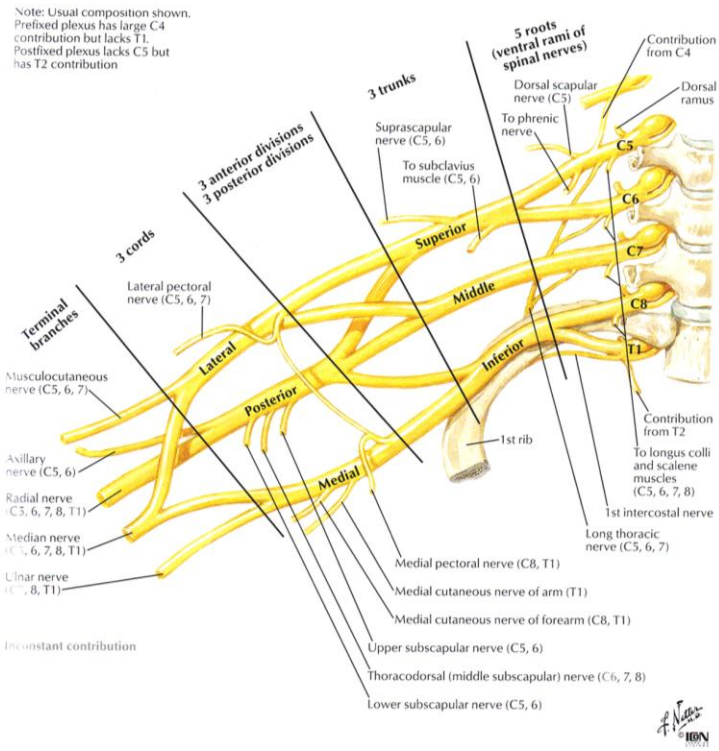
The brachial plexus supplies all of the motor and almost all of the sensory function of the upper extremity. The remaining area the skin over shoulder is supplied by the descending branches of cervical plexus, and posterior medial aspect of arm, extending nearly to the elbow is supplied by medial cutaneous nerve of the arm and the intercostobrachial branch of second intercostal nerve.

Plexus is formed from the anterior primary rami of 5th, 6th, 7th and 8th cervical and 1st thoracic nerve and frequently receives small contributing branches from the fourth cervical and second thoracic nerve. After these nerves leave their respective intervertebral foramina, they proceed anterolaterally and caudally to occupy the interval between the anterior and middle scalene muscle, where they unite to form three trunks, thus initiating the formation of proper plexus. These trunks emerge from the interscalene space at the lower border of these muscles and continue anterolaterally and inferiorly to converge toward the upper surface of first rib, where they are closely grouped cephaloposterior to the subclavian artery.

At the lateral edge of the rib, each trunk divide into an anterior and posterior division, each of which passes inferior to the mid portion of clavide to enter the axilla through its apex. These divisions by which fibres of the trunk reassemble to gain the ventral and dorsal aspects of the limb reunite within the axilla to form three cords the lateral, medial and posterior named because of their relationship with the second part of axillary artery.

At the lateral border of pectoralis minor, the three cords break upto give rise to peripheral nerves of the upper extremity.The lateral cord given off the lateral head of median nerve, lateral pectoral nerve and musculocutaneous nerve.

Figure - 1 : Anatomy of Brachial Plexus



ANATOMY OF BRACHIAL PLEXUS BLOCK

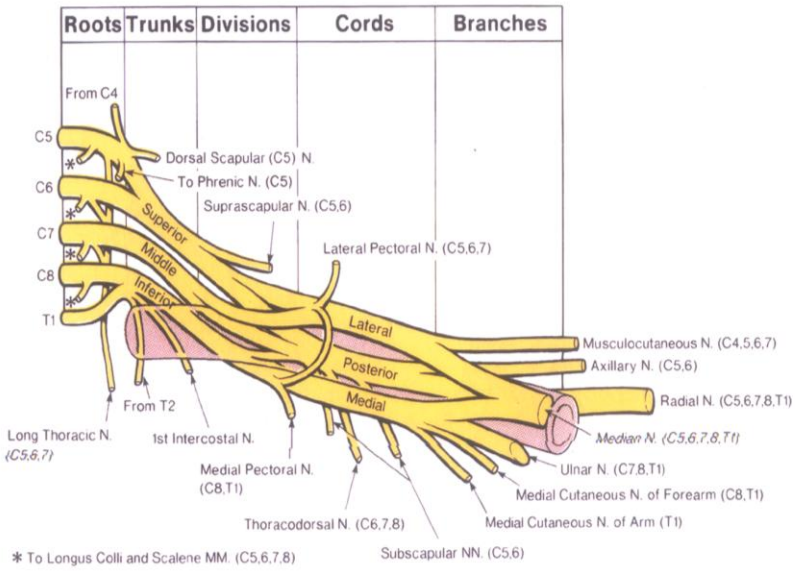


FIG. Roots, trunks, divisions, cords, and branches of brachial plexus. Note also relationship to subclavian artery. Note that the intercostobrachial nerve is not shown in this diagram. N, nerve; M, muscle.

The medial cord gives off the medial head of median nerve, median cutaneous nerve of arm, medial pectoral nerve and ulnar nerve.The posterior cord gives off the upper of lower subscapular nerve, nerve to Lattissimus Dorsi, Radial nerve and axillary nerve (Circumflex nerve).

Livingstone and Werthein originally pointed out, and Winnie has refocused our attention on, the fascial barriers that surround these structure. The prevertebral fascia divides to invest the anterior and middle scalene muscles and then fuses at the lateral margins to form an enclosed interscalene space. Therefore, as the nerve roots leave the transverse processes, they emerge between the fascia that covers the anterior and middle scalene muscle, and in their descent toward first rib to form trunk of the plexus, the roots may be considered sandwiched between anterior and middle scalene muscles, the fascia of which serves as "Sheath" of plexuses. As the root passes through this space they converge to form the trunk of the brachial plexus and together with subclavian artery, invaginate the scalene fascia which form subclavian perivascular sheath. This, in turn, becomes the axillary sheath as it passes under the clavicle.[20]

Branches from roots : The nerve (of Bell) to the serratus anterior from C5, C6 and C7. Dorsalis scapulae nerve from C5. Muscular branches to the longus cervicis (C5-C8) and the three scalene (C5-C8), the rhomboids (C5) and a branch to the phrenic nerve (C5).

Branches from trunks : Suprascapular nerve (C5 and C6) nerves to subclavius (C5 and C6).

Branches from cords :

From lateral cord	Lateral Pectoral (C5-C7)
	Lateral head of the Median (C5-C7)
	Musculocutaneous (C5, C6, C7)
From posterior cord	Upper and lower subscapular nerves (C5 and C6)
	Thoracodorsal nerve to the lattissimus dorsi (C6, C7, C8,)
	Axillary (C5 and C6)
	Radial (C5, C6, C7, C8, and T1)
From Medial cord	Medial head of Median (C8, T1)
	Medial Pectoral (C8, T1)
	Medial Cutaneous of the forearm (C8, T1)
	Medial cutaneous of the arm (T1)
	Ulnar (C8, T1)

Approaches to bronchial plexus block

(1) Supraclavicular approach

(2) Axillary approach

(3) Inter scalene approach

(4) Subclavian perivascular approach

SUPRACLAVICULAR APPROACH

The Kulenkempf and Hirschel in 1911 were the first to describe percutaneous method of blocking the brachal plexus. The technique consisted of injected local anaesthetic around brachial plexus as it crosses the first rib via a supraclavicular approach. Various modifications have been described since their original report in an attempt to increase the success rate and reduce the rate of complications.

TECHNIQUE[21]

(1) Position :

The patient should lie supine, without a pillow arms at the side and head turned slightly to the opposite side. The shoulder should be depressed caudad and posterior by gentle pressure on relaxed shoulder. This posterior displacement of the shoulder can be exaggerated by molding the shoulders over a roll placed between the scapulae.

(2) Anatomical landmark :

The interscalene groove is palpated by rolling the finger back from sternocleidomastoid muscle and over the belly of anterior scalene muscle because the brachial plexus makes its exit at lateral border of anterior scalene muscle. Usually this point is approximately at the middle of clavicle, 1.5 - 2 cm from the lateral border of clavicular head of sternocleidomastoid muscle. The subclavian artery is often palpated in supraclavicular fossa.

Figure – 2 : Supraclavicular block

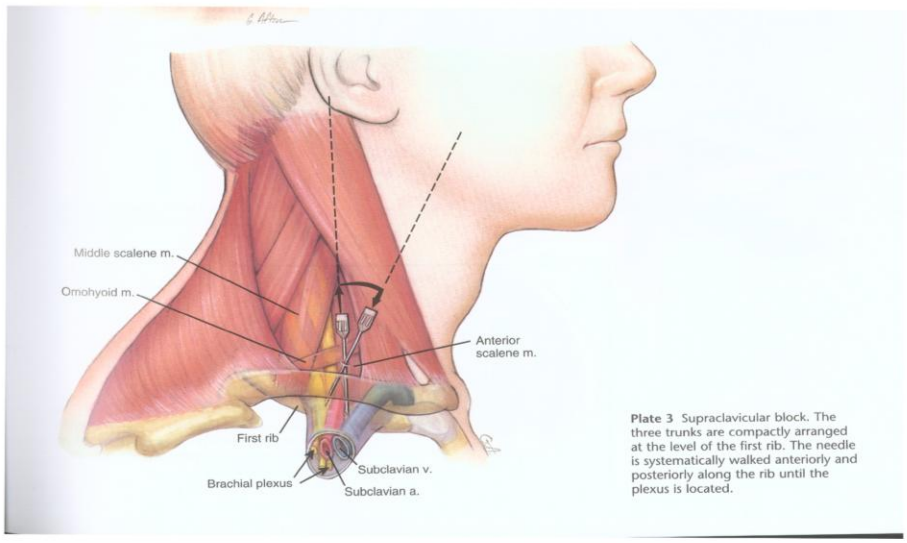


Plate 3 Supraclavicular block. The three trunks are compactly arranged at the level of the first rib. The needle is systematically walked anteriorly and posteriorly along the rib until the plexus is located.

SUPRACLAVICULAR BLOCK

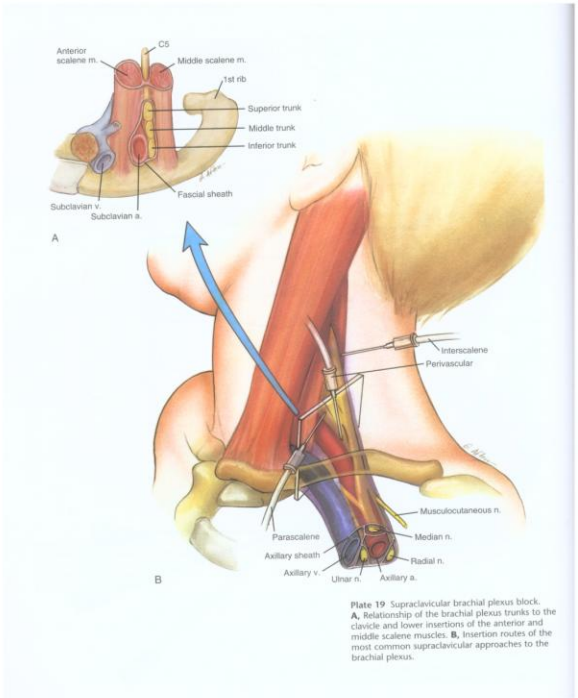


Plate 19 Supraclavicular brachial plexus block. **A,** Relationship of the brachial plexus trunks to the clavicle and lower insertions of the anterior and middle scalene muscles. **B,** Insertion routes of the most common supraclavicular approaches to the brachial plexus.

PUNCTURE POINT :

It lies at the middle of clavicle subclavian artery is palpated and the needle is inserted immediately cephaloposterior to the pulsating artery. If neither artery nor interscalene groove is palpable, a point is taken approximately 2 cm along a line marked superior to midpoint of and perpendicular to the clavicle. In a patient with a protuberant clavicle or in whom it is difficult to achieve adequate posterior displacement of shoulder, this point should be taken nearer to 3 cm superior to the clavicle.

PUNCTURE :

After disinfecting and skin wheal infiltration a 23 G 1.5" needle is inserted through the skin wheal. Keeping the thumbs on the arterial pulsation of subclavician artery and advanced slowly cauded, rolled slightly medially and posteriorly. The needle makes an angle of 45° with the table and 15° with clavicle.

The following are the advantages of this first orientation of needle. Safety of the situation of the needle tip distant from the pleural dome and subclavian artery. From this initial position the needle is redirected medially to stimulate the brachial plexus. The following are the observable stimulation.

- Superior trunk evokes contraction of bicepbrachii and deltoid muscle, elbow flexion and abduction of the arm.
- Middle trunk evokes contraction of the triceps brachii muscle and elbow extension.
- Division and cord evokes flexion pronation of hand and digit flexion in conjugation with pectoral contraction.

Movement of the abdomen can be seen from stimulation of the phrenic nerve. They imply withdrawal and redirection of the needle.

These motor responses are obtained at depth of 2-4 cm. As soon as the skin been punctured, the paraesthesia elicited and after confirmation local anaesthetic is injected. Onset and extension of blockade defined on the site of injection. Complete block occurs within 5 min for axillary nerve and with in 20 min for radial nerve following injection of anaesthetic on superior and medial trunk.

INDICATION :

It produces rapid, reliable anaesthesia for surgical procedures of upper extremity.

Areas blocked are – arm, forearm and hand except area over tip of shoulder (C3, C4) and inner aspect of upper arm (T2, intercostobrachial nerve).

The block is performed with the arm at the side thus avoiding movement in painful conditions.

It produces anaesthesia for manipulation and procedures on upper part of arm and with supplemental block.

CONTRAINDICATION :

- General – patient refusal, allergy, disorder of hemostasis, preexistent neurologic deficit, respiratory failure, infection at site.
- Specific – particular stature (short neck, stiffneck) associated disease – goitre, radiotherapy sequele, past history or cervical node resection, contralateral recurrent laryngeal nerve palsy.

COMPLICATIONS[22]

Vascular puncture :

Internal jugular vein may be punctured at skin wheal infiltration. Simple digital compression is required before continuing, the likelihood of arterial puncture implies not to pinpoint behind and too medial from midclavicle. Best is to withdraw and redirect the needle when perceiving artery pulsation at the needle tip.

Pleural puncture :

The most significant complication of supraclavicular approach for blocking brachial plexus is development of pneumothorax. The incidence of pneumothorax is 5-6 percent with this technique and much higher inexperienced hands.

A pneumothorax must be suspected when there is dyspnoea, cough or pleuritic chest pain but the diagnosis can be confirmed only by chest x-ray.

Phrenic nerve block :

Phrenic nerve block occurs in 40-60% of patient because of spread of local anaesthetic to the anterior surface of anterior scalene muscle. The effect is avoided if anaesthetic is deposited deep on the middle trunk on division or cord. This is rarely symptomatic. Radiographic confirmation may be obtained.

Recurrent laryngeal nerve block :

It causes transient dysphonia, occurs in 1% of case and only on the right side because recurrent laryngeal nerve loops around the subclavian artery on the right side and arch of aorta on the left.

Nerve damage or neuritis :

It results from the needle trauma or faulty positioning of anaesthetised arm preoperatively may be the cause. Other remote causes include excessive tourniquet time, concentrated solution with vasoconstrictor and susceptible host tissue[23].

Horner's syndrome :

It consists of ptosis, miosis, anhydrosis and enophthalmos. It usually follows stellate ganglion block. It is found in 10% of cases, after interscalene block.

Toxic reaction to drug :

It is likely to occur if there is over dosage of drug or inadventent intravascular injection is made, but can be avoided with proper negative aspiration test before drug injection.

PHYSIOLOGY OF PAIN[24,25,26]

The International Association for Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Pain is an unpleasant sensation localized to a part of the body. Any pain is accompanied by anxiety and the urge to escape or terminate the feeling. Acute pain is characteristically associated with behavioral and stress responses consisting of increased blood pressure, pupillary dilatation and increase plasma cortisol level.Many patients experience pain in the absence of noxious stimuli.

It is therefore clinically useful to divide pain into two categories.

(1) Acute pain : Which is primarily due to nociception.

(2) Chronic Pain : Which may be due to nociception but in which psychological and behavioral factors often play a major role.

Pain can also be classified according to :

(1) Pathophysiology (e.g. nociceptive or neuropathic pain)

(2) Etiology (e.g. postoperative or cancer pain)

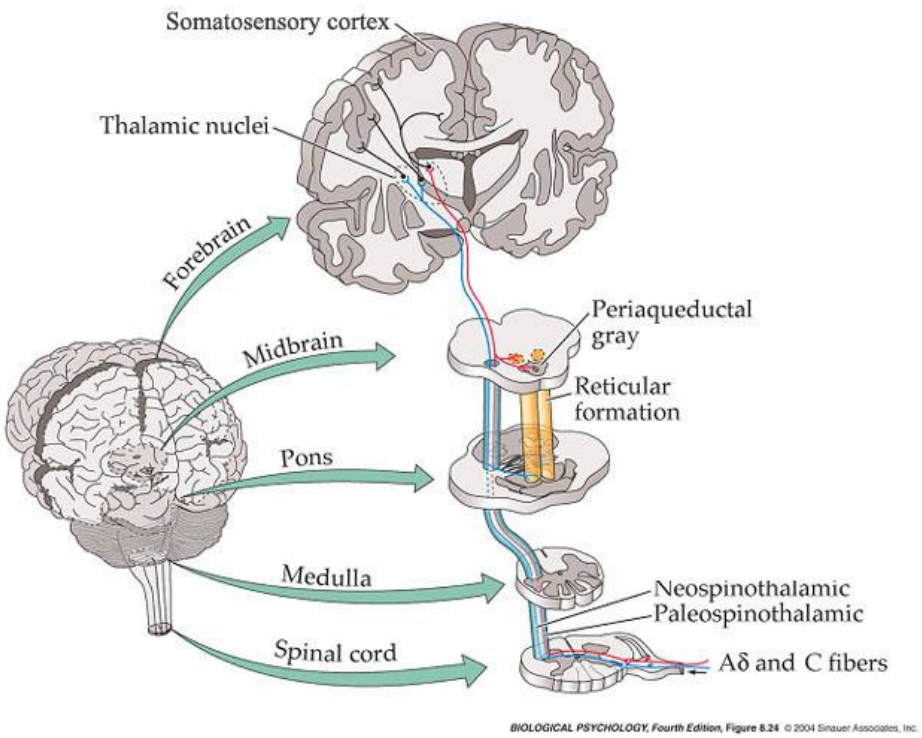
(3) Affected area (e.g. headache or low back pain)

Nociceptive pain is due to activation or sensitization of peripheral nociceptiors, specialized receptors that transduce noxious stimuli.Neuropathic pain is the result of injury or acquired abnormalities of peripheral or central neural structures.

PAIN PATHWAYS:[24]

Pain is conducted along three neuronal pathways that transmit noxious stimuli from the periphery to the cerebral cortex. Primary afferents are located in the dorsal root ganglia, which lie in the vertebral foramina at each spinal cord level. Each neuron has a single axon that bifurcates, sending one end to the peripheral tissue it innervates, and the other into dorsal horn of spinal cord. In the dorsal horn, the primary afferent neuron synapses with a second order neuron whose axon crosses the midline and ascends in the contralateral spinothalamic tract to reach the thalamus. Second order neuron synapse in thalamic nucleus with the third order neuron which in turn sends projections through internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex.

Figure-3 Pain pathways



FIRST ORDER NEURONS :

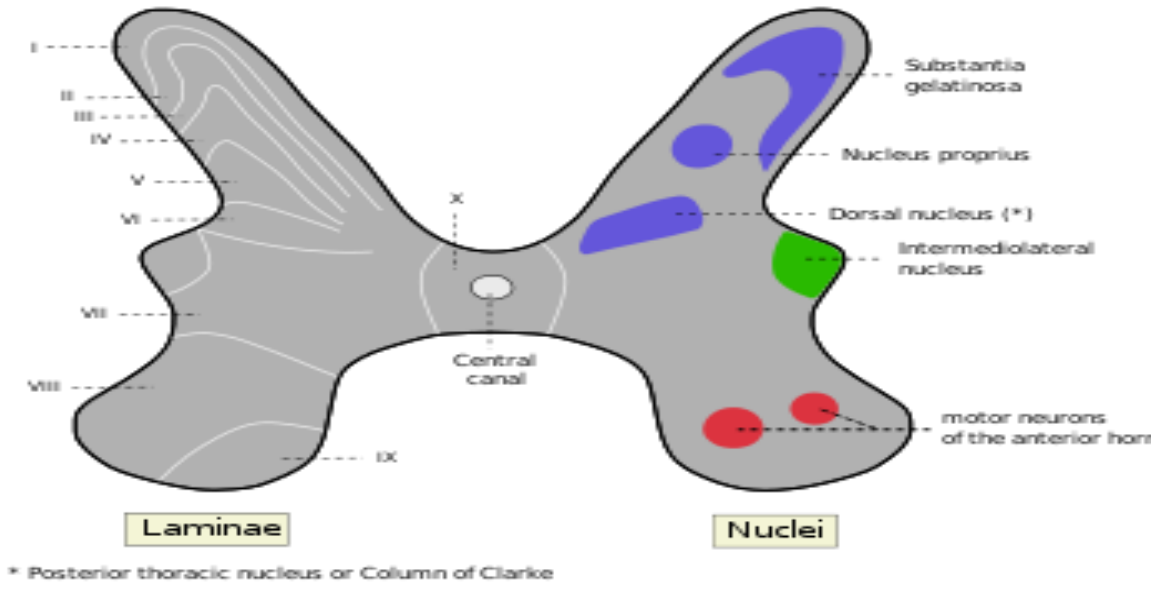
The majority of first order neurons send the proximal end of their axons into spinal cord via the dorsal (sensory) spinal root at each cervical, thoracic, lumbar, and sacral level.Some unmyelinated (C) fibres have been shown to enter the spinal cord via the ventral (Motor) root.

SECOND ORDER NEURONS :

As afferent fibres enter the spinal cord, they segregate according to size, with large, myelinated fibres becoming medial and small unmyelinated fibres becoming lateral. Pain fibres may ascend or descend one to three spinal cord segments in Lissauer's tract before synapsing with second order neurons in the gray matter of the ipsilateral dorsal horn. In many instances they communicate with second order neurons through interneurons.

Spinal cord gray matter was divided by Rexed ino 10 laminae. The first six laminae which make up the dorsal horn receive all afferent neural activity and represent the principal site of modulation of pain by ascending and descending neural pathways.

Figure-4 Rexed Laminae



Second order neurons are either nociceptive specific or wide dynamic range (WDR) neurons. Nociceptive specific neurons receive only noxious stimuli, but WDR neurons also receive non noxious afferent input from A beta, A delta and C fibres.

Most nociceptive C fibres send collaterals to, or terminate on, second order neurons in Lamina I, II and to a lesser extent Lamina V. Nociceptive A delta fibres synapse mainly in lamina I, V and to a lesser extent lamina X. Lamina I responds primarily to noxious (nociceptive) stimuli from cutaneous and deep somatic tissue. Lamina II, also called substantia gelatinosa, contains many interneurons and is believed to play a major role in processing and modulating nociceptive input from cutaneous nociceptors. It is also of special interest because it is believed to be a major site of opioid action.

Visceral afferents terminate primarily in Lamina V and to a lesser extent in Lamina I. These two laminae represent points of central convergence between somatic and visceral inputs. Lamina V responds to both noxious and non noxious sensory input and receive both visceral and somatic sensory input as manifested clinically as referred pain. Compared with somatic fibres, visceral nociceptive fibres are fewer in number, more widely distributed, proportionately activate a large number of spinal neurons and are not organized somatotopically.

Diameters of different nerve fibres (in μm)

Type-A	20-1
Type-B	<3
Type-C	Unmyelinated

(a) The Spinothalamic Tract:

The axons of most second order neurons cross the midline close to their level of origin to the contralateral side of the spinal cord before they form the spinothalamic tract and send their fibres to the thalamus, the reticular formation, the nucleus raphe magnus and the periaqueductal gray matter (PAG).

The spinothalamic tract, which is classically considered the major pathway, lies anterolaterally in the white matter of the spinal cord. This ascending tract can be divided as lateral and medial. The lateral spinothalamic (neospinothalamic) tract projects mainly to the ventral posterolateral nucleus of the thalamus and carries discriminative aspect of the pain such as location, intensity and duration. The median spinothalamic (paleospinothalamic) tract project to the medial thalamus and is responsible for mediating the autonomic and unpleasant emotional perceptions of pain. Some spinothalamic fibres also project to the peri-acqueductal gray and thus may be an important link between the ascending and descending pathways. Collateral fibres also projects to the reticular activating system and hypothalamus, these are likely responsible for the arousal response to pain .

(b) Alternate Pain Pathways:

As with epicritic sensation, pain fibres ascends diffusely, ipsilaterally and contralaterally. The spinoreticular tract is thought to mediate arousal and autonomic response to pain. The spinomesencephalic tract may be important in activating antinociceptive, descending pathways, because it has some projection to peridaqueductal gray. The spinohypothalamic and spinotelencephalic tracts activate the hypothalamus and evoke emotional behavior. The spinocervical tract ascends uncrossed to the lateral cervical nucleus, which relays the fibres to the contralateral thalamus and this is a major alternative pathway.

(c) Integration with the sympathetic and motor systems :

Somatic and visceral afferents are fully integrated with skeletal motor and sympathetic systems in the spinal cord, brain stem and higher centers. Afferent dorsal horn neurons synapse both directly and indirectly with anterior horn motor neurons. These synapses are responsible for reflex muscle activity whether normal or abnormal that is associated with pain. In a similar fashion, synapses, between afferent nociceptive neurons and sympathetic neurons in the intermediolateral column result in sympathetically mediated reflex vasoconstriction, smooth muscle spasm and the release of catecholamines, both locally and from the adrenal medulla.

THIRD ORDER NEURONS:

Third order neurons are located in the thalamus and send fibers to somatosensory areas I and II in the postcentral gyrus of the parietal cortex and the superior wall of the sylvian fissure, respectively. Perception and discrete localization of pain take place in these cortical areas. Although most neurons from the lateral thalamic nuclei project to the primary somatosensory cortex, those from the intralaminar and medial nuclei project to the anterior cingulate gyrus and likely mediate the suffering and emotional components of pain.

CHEMICAL MEDIATORS OF PAIN :

Several neuropeptides and excitatory amino acids function as neurotransmitters for afferent neurons mediating pain.

Table-1 Chemical Mediators of Pain

Neurotransmitters	Receptor	Effect of nociception
Substance P	NK-1	Excitatory
Calcitonin gene related peptides		Excitatory
Glutamate	NMDA, AMPA, Kainite, Quisqualate	Excitatory
Aspartate	NMDA, AMPA, Kainite, Quisqualate	Excitatory
Adenosine triphosphate	P1,P2	Excitatory
Somatostatin		Inhibitory
Acetylcholine	Muscarinic	Inhibitory
Encephalins	k, δ, μ	Inhibitory
B endorphins	k, δ, μ	Inhibitory
Norepinephrine	α2	Inhibitory
Adenosine	A1	Inhibitory
Serotonin	5HT1(5-HT3)	Inhibitory
GABA	A, B	Inhibitory
Glycine		Inhibitory

PHYSIOLOGY OF OPIOD RECEPTORS[27] :

In 1973, three independent teams of investigations described the presence of "Opioid receptors" in nervous tissue and hypothesized that endogenous substances probably stimulate this structure. At present three receptors are identified μ(mu), k (Kappa), δ (Delta)

CHARACTERISTICS OF OPIOID RECEPTORS :

Table-2 Characteristics of opioid receptors

	μ	δ	κ
Endogenous LIGAND	Enkephalin B Endorphin	Enkephalin	Dynorphin
Exogenous agonist ligand	Morhpine Phenyl Piperadine	DPDPE DADLE	Butorphanol and U50488
Antagonist	Naloxone and Naltrexone	Naloxone and Naltrexone	Naloxone and Nalmefene
Subtype	1,2,3	1,2,3	1,2,3
G protein couple	Yes	Yes	Yes
Adenylate cyclase	Inhibitor	Inhibitor	Inhibitor
Voltage dependent calcium channel	Inactivates	Inactivates	Inactivates
Potassium channel conduction	Increase	Increase	
Action	Analgesia Sedation Respiratory depression Miosis Bradycardia Nausea, Vomiting Decreased GI Motility	supraspinal analgesia respiratory depression	spinal analgesia diuresis dysphoria respiratory depression.

ENDOGENOUS OPIOIDS [28]:

Hughes et al described two brain pentapeptides, methionine enkephalin and leucine enkephalin as having potent affinity for opiate binding site.Later they also described B endorphin and dynorphine as having similar actions.

High concentration of B endorphin occurs in the pituitary gland (anterior and intermediate lobes greater than posterior lobe) and in medial basal and arcuate region of hypothalamus.

Enkephalins are distributed in amygdala, globus pallidus, striatum, hypothalamus, thalamus, brain stem and spinal cord dorsal horn Lamina I, II and IV that receive afferent nociceptive information. Enkephalins have also been isolated in peripheral nervous system, peripheral ganglia, ANS, adrenal medulla as well as GI tract and plasma.

Dynorphine is found in hypothalamo neurohypophyseal axis and other CNS areas of nociception; the periaqueductal grey area, limbic system, thalamus and Lamina I and V of the dorsal horn in the spinal cord.

Apart from role of endogenous opioid in perception of pain, other roles have also been identified such as antidiuresis, free water diuresis, modulation of respiratory responses to various stimuli and drugs and in the cardiovascular depression seen in shock.

Recent advances in opioid receptors a new opioid receptor was identified in rat, mouse and man and it was designated as 'orphan' opioid receptor (ORL1). Many subtypes of this receptors have been assayed recently.

MECHANISM OF ANALGESIA :

Opioid receptors belong to the super family of G protein coupled receptors. Studies indicate both presynaptic (indirect) and postsynaptic (direct) facilitatory and inhibitory actions of opioids on synaptic transmission in many regions of the nervous system. The Opioid receptor activated G protein effector system can divided into two categories :

(1) Short term effectors (K+ and Ca2+ channels).

(2) Long term effectors involving second messengers such as adenylate cyclase / cyclic adenosine monophosphate (cAMP).

Both mu & delta receptors activate K+ channels and all opioids receptor types can inhibit the opening of voltage – dependent Ca2+ channels. Changes in cAMP may underlie opioid – induced modulation of the release of neurotransmitters such as substance P.

Decrease in Ca2+ influx can decrease neurotransmitter mobilization and release. Opioid induced changes in Ca2+ concentration are likely to be a component of the mechanism of opioid analgesia.

Numerous studies demonstrate opioid action and behaviorally defined analgesia in many CNS sites. These include amygdala, the mesencephalic-reticular formation, the peri-aqueductal gray matter, and the rostral ventral medulla. Opioids acts at the periaqueductal gray area, influence through direct nerval connections, the rostral ventromedial region of the medulla. This region of the medulla in turn modulates nociceptive transmission neurons in the dorsal horn of the spinal cord. The integrity of such neurotransmitter systems connecting the pain inhibiting system in the brain to the spinal cord is necessary for opioid to exert its full analgesic action. Opioid application at the spinal cord produces analgesia at the level of administration.

Opioids act on nerve synapses either presynaptically (as neuromodulators) or postsynaptically (as neurotransmitters). The substantia gelatinosa of the spinal cord possesses a dense collection of opioid receptors. Direct applications of opioids to these receptors create intense analgesia. Spinal cord presynaptic substance P release in primary sensory neurons is inhibited by mu, kappa, and delta agonist and is one of the neuroaxial mechanism of opioid analgesia.

Opioids inhibit neuronal excitation of the dorsal horn in response to painful sharp stimulation, and sensations via A delta fibres are reduced. Excitatory post synaptic potential summation is also blocked by opioids in the dorsal horn blocking the development of dull persistent pain transmitted via C fibres. Patient responses to surgery are easier to control with opioids before rather than after stimulation. Opioids may also inhibit the early expression of DNA that is integral to transforming cellular characteristics necessary for the development of chronic or persistent pain.

Opioids may also produce some analgesia via peripheral mechanisms outside the CNS.

(1) Opioid receptors located on primary afferent neurons are likely sites of action.

(2) Opioid agonists produce a local anaesthetic like effect on the surface of excitable cell membranes.

PHYSIOLOGICAL EFFECTS OF POSTOPERATIVE PAIN :

A noxious stimulus produces local tissue damage and consequent release of chemical mediators of pain.

Prostaglandin, histamine, serotonin, bradykinin, 5-hydroxy tryptamine, substance P and a generation of noxious stimuli (produced by nociceptors) are transmitted by A and C fibres. From there some impulses pass to the anterior and anterolateral horns to provoke segmental reflex responses. Others are transmitted to

higher centres via the spinothalamic and spinoreticular pathways and produce suprasegmental and cortical responses.

Suprasegmental reflex responses cause increased muscle tone and spasm causing increase in O2 consumption. It also increases sympathetic tone causing tachycardia, increased stroke volume, cardiac work and myocardial oxygen consumption.

SIDE-EFFECTS OF UNTREATED POSTOPERATIVE PAIN[29]:

(1) Pulmonary function :

In the postoperative period, pain is widely known to impair coughing and deep breathing, leading to small airway closure intrapulmonary shunting, and hypoxemia.

Postoperative deterioration in pulmonary function appears to be directly related to be proximity of the surgical incision to the diaphragm.

Table-3 Factors that influence risk of post operative pulmonary complications

Factors	Effect	Complications
Pain, Spasm Paralysis	Reduced FRC	Thromboembolism
Reduced efficiency of Ventilation	Airway closure	V/Q mismatch
Stagnant secretion	Atelectasis	
Infection		Hypoxemia

(2) Neuroendocrine Response :

Surgical trauma and postoperative pain evoke an endocrine response characterized by increased level of cortisol, glucagon and catecholamine.

The stress induced changes seen after injury can be considered as a neurophysiological reflex response mediated via both the somatosensory and the sympathetic nervous system.

(3) Cardiovascular : Pain causing sympathetic stimulation resulting in tachycardia, increased stroke volume, increased cardiac work and increased myocardial oxygen consumption. This coupled with hypoxemia results in an increased risk of myocardial ischaemia or infarction.

(4) Thromboembolic Phenomena :

Decreased ambulation due to pain results in venous stasis, increased risk of deep vein thrombosis and pulmonary embolism.

(5) Gastrointestinal Function :

Irrespective of the duration of surgery the stomach, small intestine and colon are atonic for different periods. Pain is believed to decrease gastrointestinal motility.

(6) Psychological Aspect :

There is a linear relationship between anxiety and postoperative pain.Increasing anxiety and fear leads to increase in pain.

FACTORS MODIFYING POSTOPERATIVE PAIN :

1. Site, nature and duration of surgery: Most severe pain is associated with thoracic, spinal, abdominal and major joint surgery of long duration.
2. Age of patient: Very young and elderly require relatively less analgesia.
3. Physiological and psychological make up of the patient.
4. Presence of complication related to surgery.
5. Anesthetic management before, during and after surgery.
6. Quality of postoperative care.

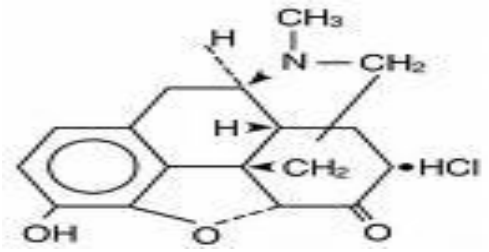
ADVANTAGES OF POST OPERATIVE ANALGESIA :

Post operative analgesia results in decreased incidence of respiratory complications, decrease in cardiovascular complication, early return in GIT motility, avoidance of a catabolic state, early ambulation and early discharge from hospital.

PHARMACOLOGY

BUTORPHANOL :[30,31,32]

Figure – 5 : Structure of Butorphanol



17 (cyclo butyl methyl) morphinan 3-14 diol dihydroxy bnutanediote

CHEMICAL STRUCTURE :

Butorphanol is a nitrogen substituted methyl group which is responsible for the mixed agonist antagonist activity and lipophilicity, whereas the hydroxyl group at C14 for additional antagonist activity, the removal of OH at C6 position also increases the analgesic activity.

CHEMICAL FORMULA :

17 (cyclobutyl methyl) morphinan - 3, 14 diol 2-3, dihydroxy butanediote. molecular weight - 477.55

MECHANISM OF ACTION :

Butorphanol is a synthetic opioid, which exerts agoinst antagonist action at μ1 receptors, and agonist action at kappa opioid receptors.

It has been found to be 7 times more potent analgesic, as compared to Morphine.

PHARMACODYNAMIC AND SYSTEMIC EFFECTS :

(1) Effect on respiration :

A parenteral dose of 2-3 mg Butorphanol produces analgesia and respiratory depression, approximately equal to 10 mg of Morphine. However, it has a ceiling effect at 30-60 mcg/kg in the degree of respiratory depression produced, which is reversible by Naloxone.

(2) Cardiovascular effects :

Haemodyanamic changes after intravenous administration, include an increase in pulmonary artery pressure, pulmonary wedge pressure, left diastolic pressure, systemic arterial pressure, pulmonary vascular resistance and increase in the cardiac workload.

(3) Git effects :

Butorphanol causes minimal to no change in the biliary tree pressure, and therefore used safely in biliary tract surgeries.

PHARMACOKINETICS :

Butorphanol binds with plasma proteins to the extent of 80%. Butorphanol crosses the placental barrier and can be detected in the breast milk. It is extremely metabolized by the liver. The major metabolite of Butorphanol, is Hydroxybutorphanol, which is mainly eliminated by the biliary system, and has a longer t½ as compared to the parent drug. Most part of the drug is excreted unchanged in the urine (70-80%), while the remaining (15%) is recovered in the faeces.

Table-4 Butorphanol pharmacokiretics based on route of administration.

Parameter	IV	IM
Onset (Min)	Rapid	10-15 min
Peak (hrs)	0.5-1	0.5-1
Duration (hrs)	3-4	3-4
Half life (hrs)	2.1-8.8	

Table-5 Adverse effects :

1.	Cardiovascular	Hypotension, is a rare side effect occurring in <1% of the population.
2.	Central; nervous system	Dizziness, confusion, euphoria, paraesthesia, hostility, dysphoria and drug dependence in <1%.
3	Dermatology	Sweating, pruritus, rash
4.	GI tract	Nausea, vomiting, dry mouth
5.	Miscellaneous	Asthenia lethargy, blurred vision and impaired urination.

CONTRA INDICATION :

Hypersensitivity to Butorphanol or any other products.

ROUTES OF ADMINISTRATION AND DOSAGE :

1. Intravenous (0.5 - 2 mg), repeated 3-4 hrly
2. Intramuscular (1-4 mg), repeated 3-4 hrly
3. Intranasal
4. Epidurally,Intrathecally
5. In brachial plexus block

USES :

(1) Premedication :

Usual dose is 2 mg, 60-90 minutes before surgery

(2) Balanced anaesthesia :

It is given as a component of balanced anaesthesia, usually 1-2 mg given I/V shortly before induction and 0.5-1 mg I/V increments are given.

(3) Regional Anaesthesia :

Butorphanol is used as on adjuvant analgesic drug in the following regional anaesthesia.

(a) Epidural blockade

(b) Brachial plexus block

(c) Spinal anaesthesia

In all the above blocks, Butorphanol when mixed with Local anesthetic agents, prolongs the duration of analgesia by 4-5 hrs.

Doses should be carefully titrated in elderly, patients with hepatic and renal, disease.

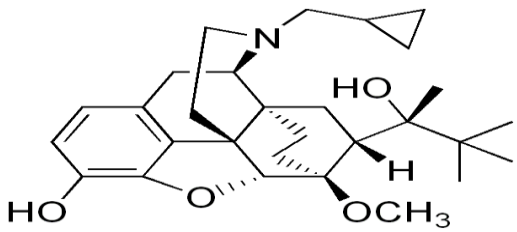
BUPRENORPHINE : [32,33,34]

INTRODUCTION

Buprenorphine (CN-L-cyclopropyl methyl oripavin) is a semisynthetics highly lipophytic ring C bridge oripavine derivative of thebaine with narcotic agonist and antagonist activity. It is 25 to 40 times more potent than Morphine in analgesic effect.

Chemical structure: Buprenorphine HCLis 17 cyclopropyl methyl α1,1-dimethyl ethyl 4,5-epoxy-18,19-dihydro 3-hydroxy 6 methoxy -2-methyl-6,14 ethanomorphinan-7 methanol hydrochloride.

Figure - 6 : Structure of Buprenorphine



PHARMACOLOGICAL ACTIONS:

(1) Central nervous system

Buprenorphine Produces typical dose related morphine like subjective effects. They are slower in onset but longer duration. Early receptor binding studies suggested that Buprenorphine was a selective mu receptor agonist. In rodents the dose response curves for Buprenorphine induced analgesia and catalepsy are bell shaped..It has a high affinity for the mu, delta and kappa receptors.

In receptor binding studies Buprenorphine behaves like an antagonist – Judged by the effect of Na++ ion affinity. Due to its no receptor agonist action it may cause symptoms of abstinence in patients who have been receiving Morphine like drugs. It antagonizes the respiratory depression produced by anaesthetic doses of Fentanyl has

Naloxone, without completely preventing opioid pain relief. Buprenorphine is effective in relieving pain moderate to severe degree associated with surgical procedures, (Abdominal, thoracic, orthopaedic and hysterectomy) cancer pain neuralgias, renal colic, labour pain and myocardial infarction. It is more potent than morphine, pethidine, and pentazocine and the duration of analgesia is longer than all. Buprenorphine is relatively free form dysphoria and psychotomimetic actions. Hallucinations was produced in only 0.9%

(2) Respiratory system

The subjective respiratory depressant effects are unequivocally slower in onset and lasts longer than those of morphine. Maximum respiratory depression is observed at about 3 hours. Respiratory depression has not been observed in critical trial. Significant respiratory depression which appeared to be dose related significant reduction in minute volume which occurred one hours after intravenous injection of respiratory stimulant Doxapram. In anaesthetized patients Buprenorphine decreases both respiratory rate and volume. In post operative period Buprenorphine produces tendency towards respiratory acidosis and small decreases in respiratory rate (15%) and minute volume (16%).

(3) Cardiovascular system

In equivalent doses all the cardiovascular effects are similar to those of Morphine. There is significant reduction in heart rate (16%) and same decreases in systolic blood pressure with only minor decrease in systolic & diastolic pressure. In surgical or myocardial infarct patients, there is dose related decrease in systolic and diastolic pressure (10 to 25%), oxygen consumption (40%), left ventricular work (19%) and heart rate (24%) as well as compensatory increase in stroke volume. There is small decrease in pulmonary artery blood pressure myocardial contractility is not

affected. It appears to be a safe analgesic for patients with a recent myocardial infarction.

(4) Alimentary system

It does not necessarily produce constipation. It causes nausea, vomiting 10 to 20%. It increase intrabilliary pressure.

REVERSIBILITY OF BUPRENORPHINE EFFECT

By narcotic antagonist.

Naloxone only partially reverses the respiratory depression produced by Buprenorphine : although this effect was temporarily reversible with a respiratory stimulant drug Doxapram. Such treatment was apparently not completely satisfactory.

TOLERANCE, PHYSICAL DEPENDENCE AND LIABILITY FOR ABUSE

In post addicts patients subcutaneous dose of Buprenorphine ranging from 0.2 mg to 2 mg. produce typical morphine like effects. Burprenorphine was given subcutaneous for 40 to 50 days in a daily dose of 8 mg. Subjects and observer identified Buprenophine as a Morphine like agent subsequent administration of Naloxone did not produce abstinence syndrome. Buprenorphine resulted in very slowly emerging signs of withdrawal indicating a very long duration of action with very slow dissociation from opiate receptor sites.Overall potential for above of Buprenorphine is less than that of morphine.

PHARMACOKINETICS

Absorption

It is rapidly absorbed after intramuscular injection peak plasma levels are equal to these achieved with intravenous injection. Absorption is variable in sublingual dose. Average peak level in 3 hours and absorption completes within 5 hours. However, analgesia is attained within 15 minutes to 20 minutes and effect last longer than plasma levels. Thus appears to be no direct relationship between plasma levels and pharmacological actions. Bioavailability after sublingual dose in 50% occur with other strong analgesics such as Morphine, Pethidine, and Pentazocine.

Precautions

It may infrequently affect respiration and hence should be used with care in treating patients with impaired respiratory function. Ambulant patients should be warn not to drive car as it can cause drowsiness. As it has antagonist properties, it may precipitate withdrawal syndrome in narcotic addicts. The intensity and duration of action may be affected in patients with impaired liver functions.It should be used with caution in patients receiving MAO Inhibitors. It is relatively contraindicated in patients with head injuries.There is no absolute contraindications. It is not at present recommended in children and pregnant patients.

Routes of administration - Sublingual Parenteral, Intramuscular, Intravenous, Subcutaneous. Through Brachial plexus block, Intrathecally, Epidurally

USES :

Analgesia :Post operative pain, premedication before surgery, component of balance anesthesia.

To reverse anaesthetic effects of fentanyl

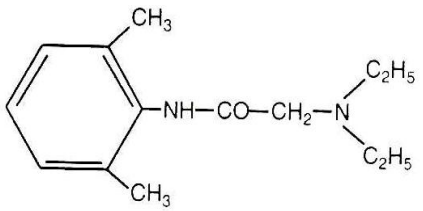
LIGNOCAINE:[35,36]

INTRODUCTION :

Lignocaine was synthesized in 1943 in Sweden, by Lofgren of AB Astra and it was introduced in the clinical practice in 1948.Lignocaine is of moderate potency and duration, but of good penetrating power and rapid onset of action. Its increased popularity for epidural anaesthesia is due to excellent penetration which renders the blockade highly successful.

CHEMICAL STRUCTURE :

Figure-7 Structure of Lignocaine



PROPERTIES:

It is an amide local anaesthetic which is soluble in water. The molecular weight is 234. Plasma protein binding is 64%. The PKa of lignocaine at 25°C is 7.86, So at physiological pH 7.4 it is 25% in nonionized form, So it has great penetrating power. It is available as hydrochloride salt and solution has pH of 6.3

The carbonate of lignocaine solution has higher pH than that of hydrochloride, thereby increasing the concentration, remarkable, penetrative powers, rapid onset of action, a high incidence of motor block, and a reduced incidence of missed segment when used for epidural anaesthesia.

Tachyphylaxis may be less evident with lignocaine carbonate than that hydrochloride.

MODE OF ACTION :

All local anaesthetics have similar mechanism of action in general by reversible blockade of sodium channel conduction.

Carbonated lignocaine has cation as the active form which acts from interior of the cell membrane. Factors contributing to enhanced effect of carbonated lignocaine over hydrochloride are :

(1) Higher pH, so concentration of uncharged base for penetration is higher.

(2) CO2 released and diffuses to the interior of cell and lower the pH, thereby increasing ionisation of the local anaesthetics.

(3) CO2 itself is having nerve blocking effect.

PHARMACOLOGICAL EFFECTS :

(1) Local :

In addition to nerve blockade it causes local vasodilatation, so absorption of drug in systemic circulation is enhanced and duration of blockade is short. Addition of adrenaline prolongs the duration of local anaesthetics by producing local vasoconstriction.

(2) Systemic

(a) Cardiovascular effects :

Lignocaine has a stabilising effect on the cell membrane of cardiac tissue. it tends to depress automaticity in abnormal or damaged fibres and thereby suppress cardiac dysrhythmias. In therapeutic doses doesnot cause consistent rate change and doesnot depress conduction in Purkinje fibre. An improvement in cardiac output and blood pressure has been observed when used in treatment of cardiac dysrhythmias.

(b) Central Nervous System :

Sedative effect of lignocaine absorbed after epidural administration is well recognized. With marked toxicity a numb tongue, circumoral pins and needles, twitching and visual disturbance, severe toxicity proceeds to convulsions and coma with respiratory and cardiac depression.

(c) Autonomic nervous system :

A weak blocking effect on adrenergic receptors.

DOSES :

The safe dose limit for lignocaine has been much disputed. The upper safe limit ascribed was 200 mg plain and 500 mg with adrenaline for an adult patient. The maximum safe dose in man is probably about 6 mg/kg possible less than this for plain solutions in vascular areas while more than this with adrenaline to less vascular areas. Toxic symptoms may occur at plasma levels of 3-5 mcq/ml but this level is not produced after a single shot epidural block.

BUPIVACAINE:[36,37,38]

INTRODUCTION :

Bupivacaine is one of the homologous series synthesized in 1957 by A.F. Ekenstam to which Mepivacaine belongs. First report of its use was made in 1963 by Telivuo. Bupivacaine is three to four times as potent as lignocaine, and considerably longer lasting.

PROPERTIES :

Bupivacaine hydrochloride an amide is readily soluble in water and has good stability. The pH of plain solution is 6.0 to 6.7 and molecular weight is 324.9. It can be stored at room temperature. It is compatible with adrenaline and can be autoclaved more than twice. Commercially available bupivacaine contains no preservative. The chemical name of bupivacaine is (DL)-1-Butyl-2-(2,6-xylocarbonyl)-piperidine.

MODE OF ACTION :

It causes reversible blockade of sodium conduction probably by dual actions on cell membrane.

(1) They act directly on receptors within sodium channels.

(2) They produce nonspecific membrane expansion.

PHARMACOLOGICAL EFFECTS :

The effects produced by bupivacaine may be :

(1) Local :

Nerve blockade and a direct effect on smooth muscle.

(2) Regional :

Loss of pain and temperature sensations, touch, motor power and vasomotor tone in the region supplied by the nerve blocked.

(3) Systemic : The chief systemic effects are :

(a) Cardiovascular system :

Gross overdose has been associated with ventricular tachycardia, fibrillation and cardiac arrest. There is good evidence, however that cardiac toxicity does not occur in subconvulsive doses or in absence of severe electrolyte disturbances or in absence of respiratory or metabolic acidosis. With a dose of 1.2 mg/kg given intravenoulsy at a rate of 4.3 mg/min there is no change in pulse rate, ECG, blood pressure and cardiac output. It causes vasodilatation in the area supplied by sympathetic nerves which are blocked.

(b) Central nervous system :

It produces sedation and light headedness and sometimes anxiety and restlessness. With marked toxicity the patient may notices a numb tongue, circumoral pins, and needles, twitching and visual disturbances. Severe toxicity proceeds to convulsions and coma with respiratory and cardiovascular depression.

(c) Autonomic nervous system :

A weak blocking action on cholinergic and adrenergic receptors.

(d) Neuromuscular junction :

It can block motor nerves if present in sufficient concentration.

(e) Hypersensitivity :

It can occur but more frequently in atopic patients in the forms of local oedema initially generalized urticaria or angioneurotic oedema with or without lymphadenopathy. Dermatitis may be encountered as delayed reaction but anaphylaxis appear very rare.

PHARMACOKINETICS :

Absorption :

A dose of local anaesthetic is absorbed into the systemic circulation. Vascularity of tissue affect the space of absorption. So, it affects the toxicity.

Distribution :

Bupivacaine has a great affinity for negatively charged protein receptor sites. At a plasma concentration of 1 mcg/ml the degree of protein binding is about 96.8% as opposed to 75% of lignocaine. Thus it has high protein binding capacity.

Blood level :

In animals 4 mcg/ml in plasma causes convulsions. The peak plasma concentration appear slowly and reaches highest between 5-30 minutes. After reaching this level it falls slowly, this explains to longer duration of action.

Placental transfer :

As bupivacaine is highly protein bound, it passes to fetus to a slower rate and is unlikely to cause fetal plasma concentration equal to that of maternal. Neonatal depression is not found with bupivacaine.

Metabolism :

It is rapidly catabolised like other local anaesthetics and chiefly metabolised in liver, metabolism involves N-dialkylation to pipecolyxylidine (PPX) which is then hydrolysed. It has a fairly rapid rate of elimination from the blood because of faster tissue uptake and rapid rate of metabolism and so, there is hardly accumulation of drug in the body even after prolonged administration and clinically found blood levels are much below the toxic dose.

Excretion : Demethylation of piperidene ring and coupling of glucuronic acid in the liver and is excreted through bile duct and kidney.

Uses :

The uses other than epidural anaesthesia are :

(1) Local infiltration anaesthesia

(2) Nerve blocks

(3) Spinal anaesthesia

(4) Epidural analgesia : labour and post-operative analgesia.

(5) Intravenous regional anaesthesia (IVRA)

Doses :

It is available in

0.5% 20 ml vial,

4 ml ampoule and

2 ml 1% ampoule

Safe dose is 2 mg/kg of body weight, wide field block and excessive surface application of local anaesthetic causes toxic reaction.

MATERIAL AND METHODS

SOURCE OF DATA:

A study was carried out in 60 patients of either sex undergoing supraclavicular brachial plexus block, using local anaesthetic agents with injection Butorphanol and Buprenorphine in department of Anaesthesiology at Shri B.M.Patil Medical college, Bijapur from Dec 2007-Jan 2009.

METHOD OF COLLECTION OF DATA:

Sample size: Considering the mean and SD of duration of analgesia as per VASscore at the end of 9 hr is 3.3±2.7 at allowable error +1, the calculated sample size n is 29.

Using statistical formula,

$$n = \frac{4\sigma^2}{L^2}$$

Hence a total number of 30 patients in each group with inclusion and exclusion criteria were selected for study, during a period of 12 months (time bound study). Patients were allocated randomly to each group by lottery method.

Inclusion criteria:

- Patients undergoing orthopaedic upper limb surgeries in the age group of 18-60 years of both sexes will be included with ASA grade I and grade II.

Exclusion criteria :

- ASA Grade-III and IV high risk patient.
- Bleeding disorders
- Cardiovascular disorders, respiratory disorders, renal disease and liver diseases.

- ❖ Circulatory instability
- ❖ Patient with known hypersensitivity to local anaesthetics
- ❖ Opiod addicts.

Statistical data:

At the end of study, all data is compiled and analyzed statistically using

- Diagrammatic representation
- Descriptive data presented as mean ± SD
- Continuous data are analyzed by paired /unpaired 't' tests and
- Chi-square test to assess the statistical difference between the two groups

PREANAESTHETIC ASSESSMENT :

Patients demographic datas like age, height, weight, history and findings of the examination of airway, cardiovascular and other systems were recorded. Routine investigation like Haemoglobin, urine sugar, Blood Urea, Creatinine, Chest X-ray, ECG were done in all patients. Patients were explained in detail about the anaesthesia procedure and drugs. All the patients were kept nil by mouth 6-8 hours pre induction. Written and informed consent were taken.

GROUPS :

All the patients were randomly allocated into two groups so that each group consist of 30 patients each.

GROUP – I :

Inj. Lignocaine hydrochloride (2%)	5-7 mg/kg
Inj. Bupivacaine hydrochloride (0.5%)	1-2 mg / kg
Inj. Butorphanol	1 mg

GROUP – II :

Inj. Lignocaine hydrochloride (2%)	5-7 mg/kg
Inj. Bupivacaine hydrochloride (0.5%)	1-2 mg / kg
Inj. Buprenorphine	100 μgm (0.1 mg)

PREMEDICATION :

All patients were pre medicated with Inj. Glycopyrrolate 4 μg/kg and Inj Ondensetron 4mg IV, given 5 minutes before surgery.

No analgesic drugs were given in pre medication.

PROCEDURE:

All patients were explained about the procedure of anaesthesia to elicit paraesthesia.

- The patient was made to lie in supine position with both arm adducted and straight. Head was turned away from the side to be blocked.

- After giving appropriate position to the patient, the wide area of supraclavicular part with neck, upper chest and upper arm was painted with sterile solution of povidone Iodine followed by spirit and then draped with sterile round towel.

- Anaesthesiologist standing at the head end of the patient with face facing toward patient's foot end, underall aseptic precaution, the pulsation of subclavian artery was palpated with thumb of one hand at 1 cm above the mid point of clavicle and the point of maximum pulsation was marked. Then a short fine needle of 23 G 1.5 inch long, attached to a 2cc syringe filled up with 2CC distilled water was held in other in pen holding fashion. Distilled water was

taken to detect inadvertent apical pleura puncture. (if pleura gets puncture, air bubble comes in syringe filled with distilled water)

- While placing the thumb on pulsation of subclavian artery, it is displaced medially, and the needle was introduced just lateral to artery at about 80^0 to the skin, 1 cm above clavicle. Then needle was advanced medially, caudally and posteriorly, till upper border of 1st rib is felt. Then needle was walked anteriorly and posteriorly on the 1st rib and patient was asked for feeling tingling at the elbow and fingers (paraesthesia). Once patient felt paraesthesia, suggestive that needle is near nerve bundle. 35 ml of drug mixture was given after careful negative aspiration.

- Immediately after drug injection, massage was done for 3 min for even distribution of drug.

MONITORING :

- Both the patient and investigator making observation were aware of drugs administered.
- Motor and Sensory blockade was evaluated at 5,10,15,20 and 25 minutes after giving drug. All vital Data like Pulse Rate, BP, Spo2, ECG were monitored. All patients were observed for complications like Intravascular Injection, Pneumothorax, Hemothorax and Horners syndrome.
- Sensory block was assessed by pin prick method.

Grade	0	=	Sharp pain
	1	=	Dull sensation (Analgesia)
	2	=	No sensation (Anaesthesia)

- Motor blockade was assessed by following scale.

Grade 0 = Normal grip strength

1 = Paresis, reduced grip strength and heaviness felt in raising arm above head.

2 = Paralysis, no grip strength, and inability to raise arm above head

POST OPERATIVE OBSERVATION :

All patient were observed for analgesia hourly until patient demanded analgesia. Duration of analgesia was noted as time taken until patient demanded analgesia. Side effects like tachycardia, bradycardia, respiratory depression, hypotension, nausea, vomiting, pruritus, urinary retention etc were also noted. Pulse rate, blood pressure, Visual analogue scale were observed every hourly for 9 hrs post operatively.

VAS (VISUAL ANALOGUE SCALE) :

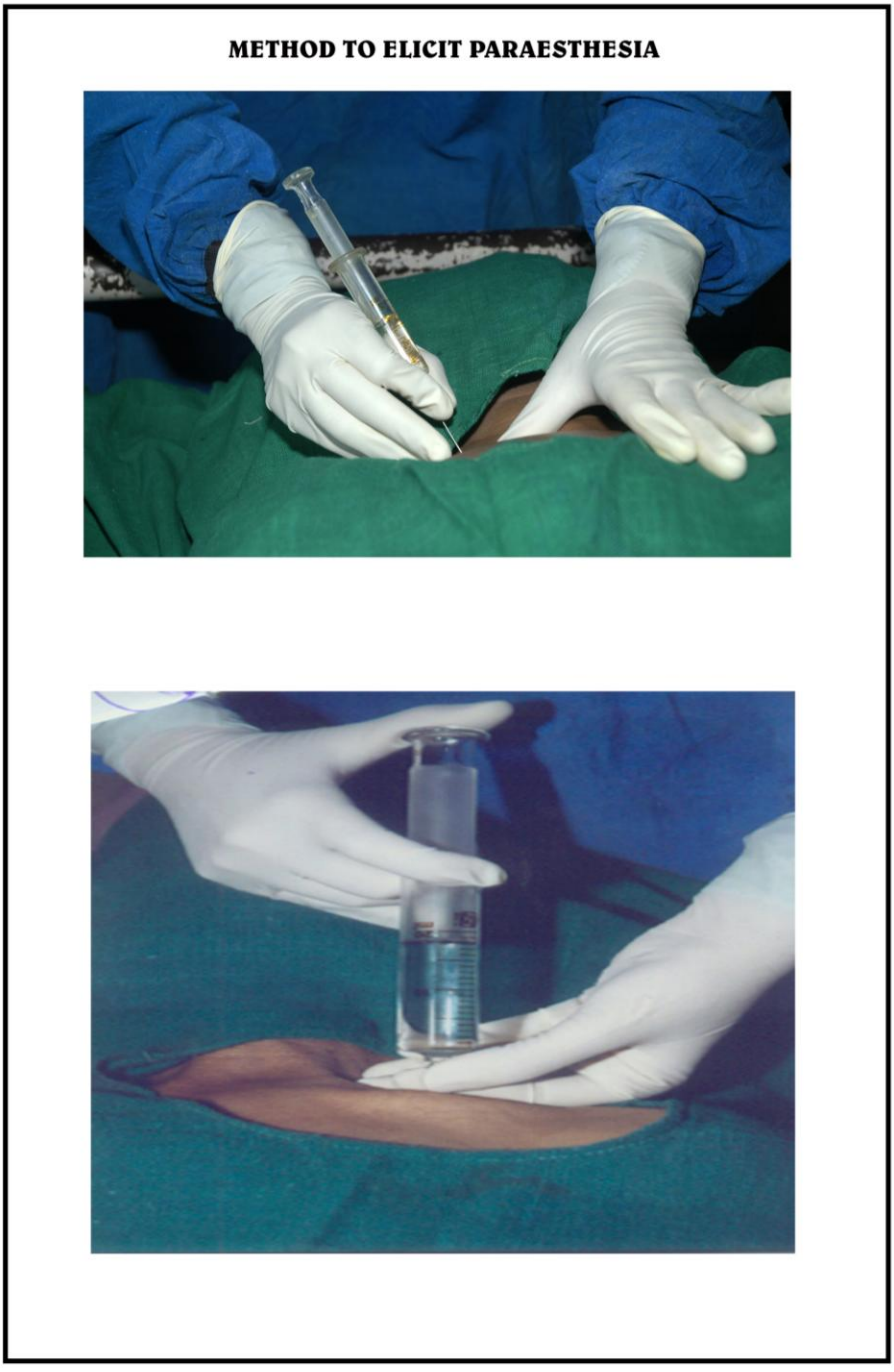
0 1 2 3 4 5 6 7 8 9 10

No Pain Excruciation pain

It is a 10 cm long slide ruler with "no pain" written at one end and "Maximum Pain" at the other. The patient slides the cursor along the ruler until it reach the level that represents the intensity of his pain. The other side of ruler is graduated over 100 mm and gives the investigator a numerical measure of the pain.

Fig – 8 : Syringes, Needles and Drugs

Figure – 8 : Method To Elicit Paraesthesia



OBSERVATION AND RESULTS

The present study of postoperative analgesia was carried out using Inj. Butorphanol (Group I) & Inj. Buprenorphine (Group II) through supraclavicular route in brachial plexus block in patients from age 18-60 yrs. The study included 60 patients who were admitted in Shri B.M.Patil Medical College &Hospital, Bijapur, between 2007-2009 undergoing upper extremity surgery in orthopedics. All the patients were randomly allocated into two groups so that each group consist of 30 patients each.

GROUP-I :

Inj. Lignocaine hydrochloride (2%)	5-7 mg/kg
Inj. Bupivacaine hydrochloride (0.5%)	1-2 mg / kg
Inj. Butorphanol	1 mg

GROUP-II :

Inj. Lignocaine hydrochloride (2%)	5-7 mg/kg
Inj. Bupivacaine hydrochloride (0.5%)	1-2 mg / kg
Inj. Buprenorphine	100 μgm (0.1 mg)

DEMOGRAPHIC DATA :

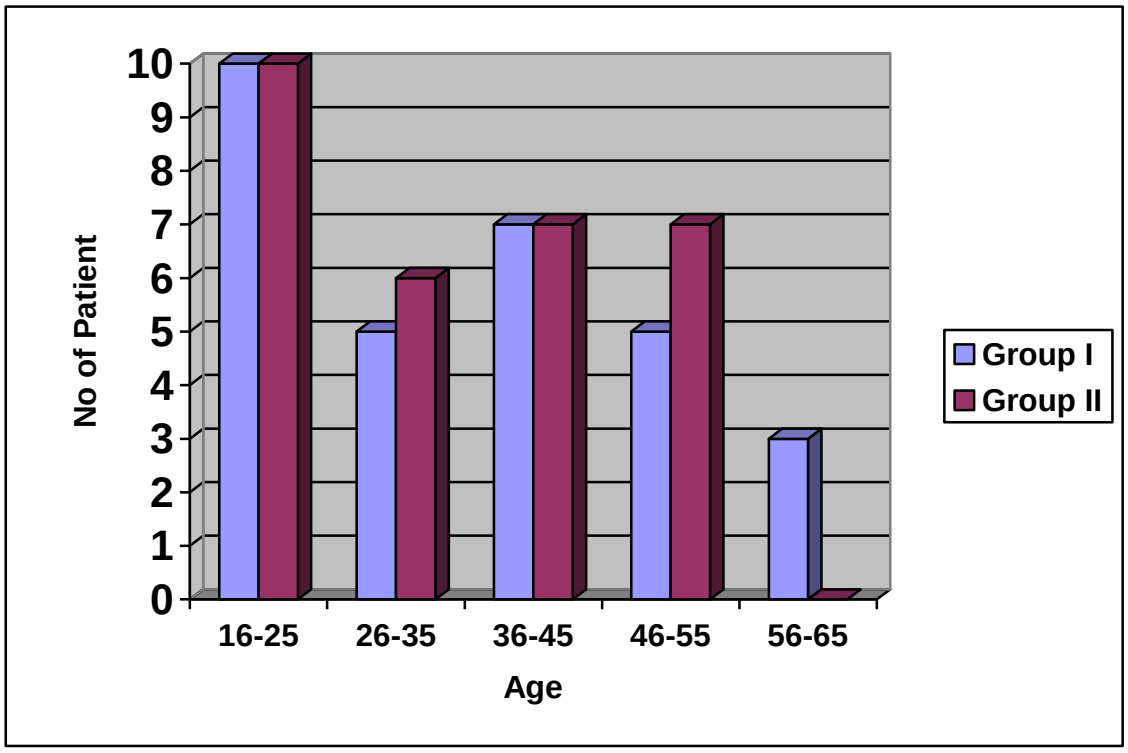
(1) AGE :

In Group-I, patient age ranged from 18-60 yrs with mean of 34.83 ± 11.58 yrs while in Group-II age ranged from 18-60 yrs with a mean of 36.43 ± 14.86 yrs. Age incidences between two groups were comparable.

Table – 6 : AGE

	Group-I (n=30) Butorphanol	**Group-II (n=30) Buprenorphine**
16 to 25	10	10
26 to 35	5	6
36 to 45	7	7
46 to 55	5	7
56 to 65	3	-
Minimum Age	18	18
Maximum	60	50
Mean	34.83 ± 11.58	36.43 ± 14.86

Figure – 10 : Age distribution



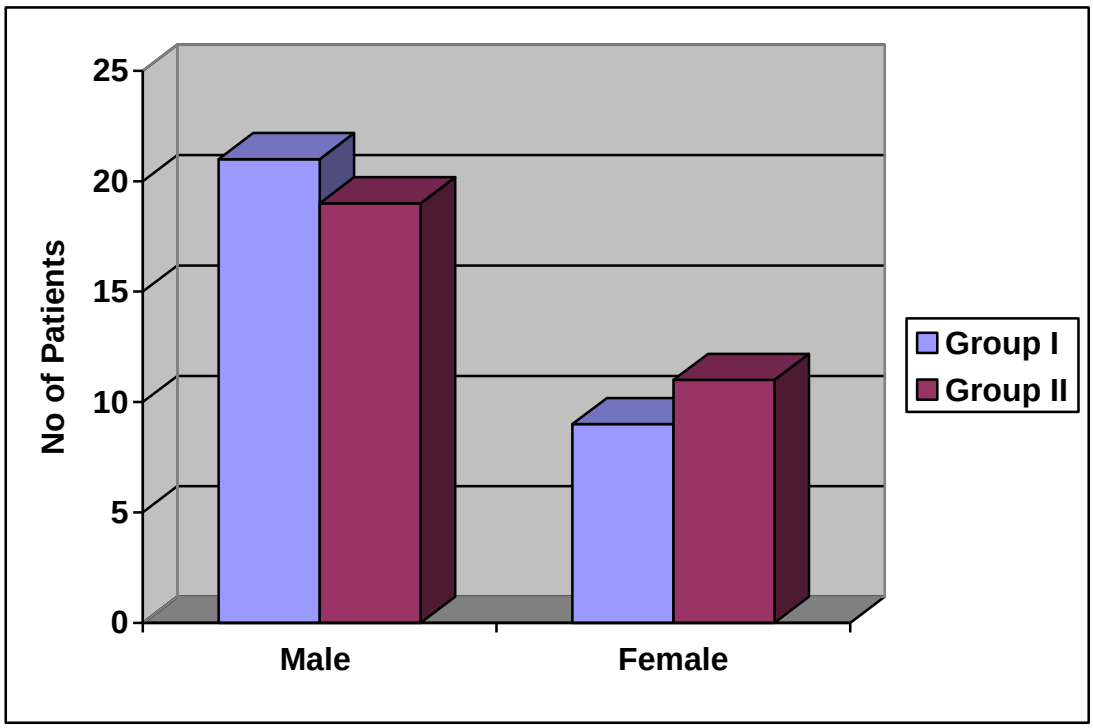
(2) SEX :

In Group-I, there were 21 male patients (71%) and 9 female (30%) with M :F ratio of 21 : 9 while in Group-II there were 19 male (63.33%) and 11 females (36.67%) with M:F ratio of 19:11. These dates have been shown in Table-7. So the demographic distribution in both these groups is comparable.

Table – 7 : SEX

Sex	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine
Male	21 (70%)	19 (63.33%)
Female	9 (30%)	11 (36.67%)
M : F	21 : 9	19 : 11
	1:2.3	1:1.7

Figure – 11 : Sex incidence



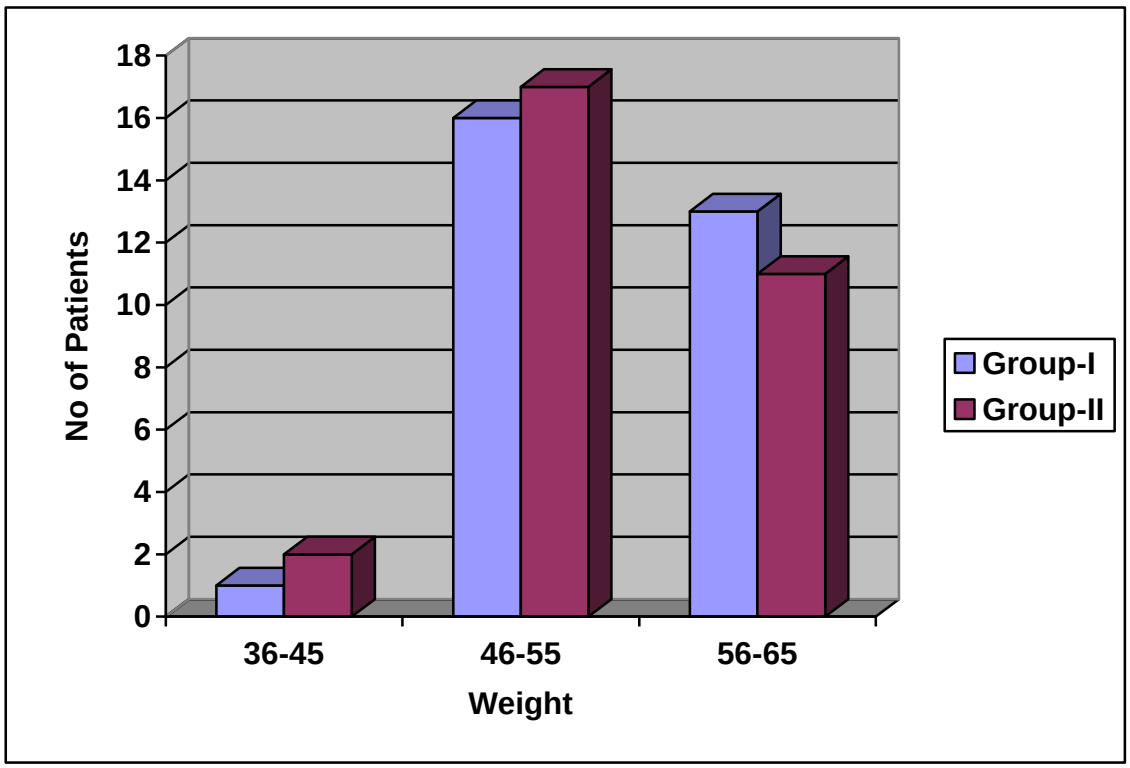
(3) WEIGHT :

In Group-I, patients weight ranged from 45-65 kg, with mean of 55.33 ± 5.56 while in Group-II, weight ranged from 45-65 kg with mean of 55.86 ± 4.89 This data is shown in Table - 8.

Table - 8 : Weight

Weight	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine
36-45	1	2
46-55	16	17
56-65	13	11
Range	45-65	45-65
Mean	55.33	55.86
S.D.	5.56	4.89

Figure - 12 : Weight



SURGICAL PROCEDURES :

All the surgical procedures were elective. Table 9 shows this distribution in both groups.

Table - 9 : Distribution Of Surgical Procedures

Surgical Procedure	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine
Open Reduction + Pinning fracture humerus	7	12
Open Reduction + Platting fracture radius	12	6
Open Reduction + Platting fracture ulna	4	1
Open Reduction Internal Fixation fracture radius & ulna	5	7
Tension Band Wiring Olecranon	1	2
Open Reduction Internal Fixation and Kwiring	1	2
	30	30

Table – 10 : Time To Onset Of Motor Blockade

Motor Time (min)	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine
1-3	0	0
4-6	13	0
7-9	17	14
10-12	0	16
13-15	0	0
Mean ± SD	6.36 ± 1.75	9.2 ± 1.32

Onset of motor blockade was 6.36 ± 1.75 in Group I and 9.2 ± 1.32 in Group II and was comparable in both the groups as the difference was t =2.0, P =3.03E-12 and Inference - HS. So Group II had delayed motor onset compared to Group I.

Figure – 13 : Onset of Motor blockade

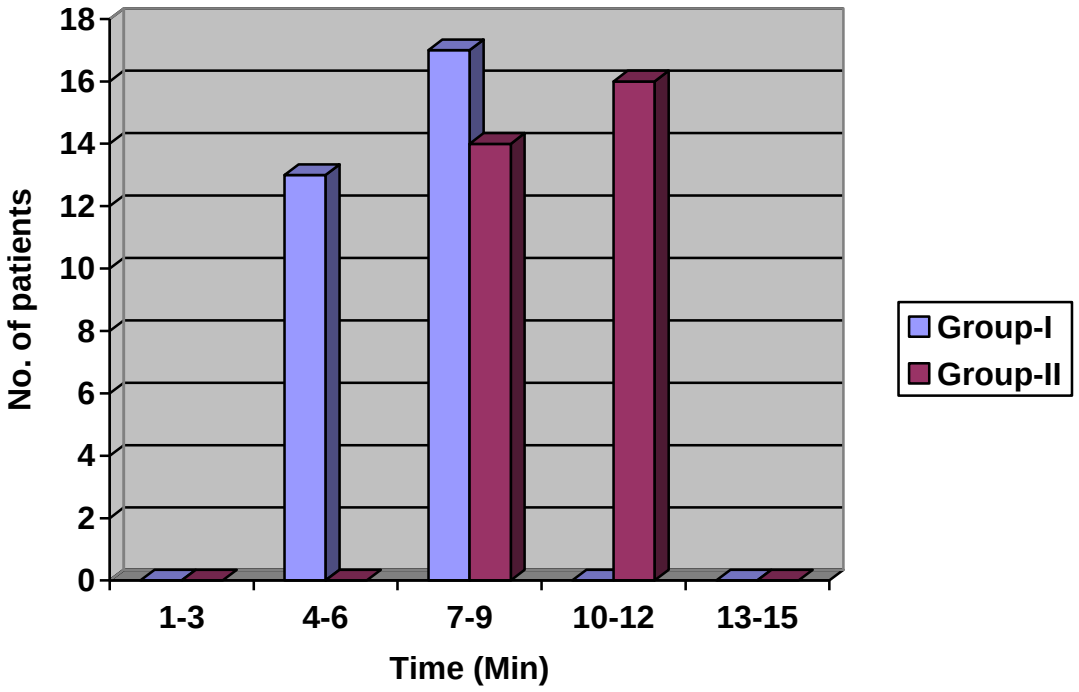


Table – 11 : Time To Onset Of Sensory Blockade

Sensory onset (in min)	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine
1-3	17	6
4-6	13	15
7-9	0	9
10-12	0	0
Mean ± SD	3.46 ± 1.00	5.23 ± 1.54
t	2.00	
P	3.21E-06	
Inference	HS	

Onset of sensory blockade was 3.46 ± 1.00 in Group I and 5.23 ± 1.54 in Group II and was comparable in both the groups as the difference was t =2.0, P =3.21E-06 and Inference - HS. So Group II had delayed sensory onset compared to Group I.

Figure – 14 : Onset of sensory blockade

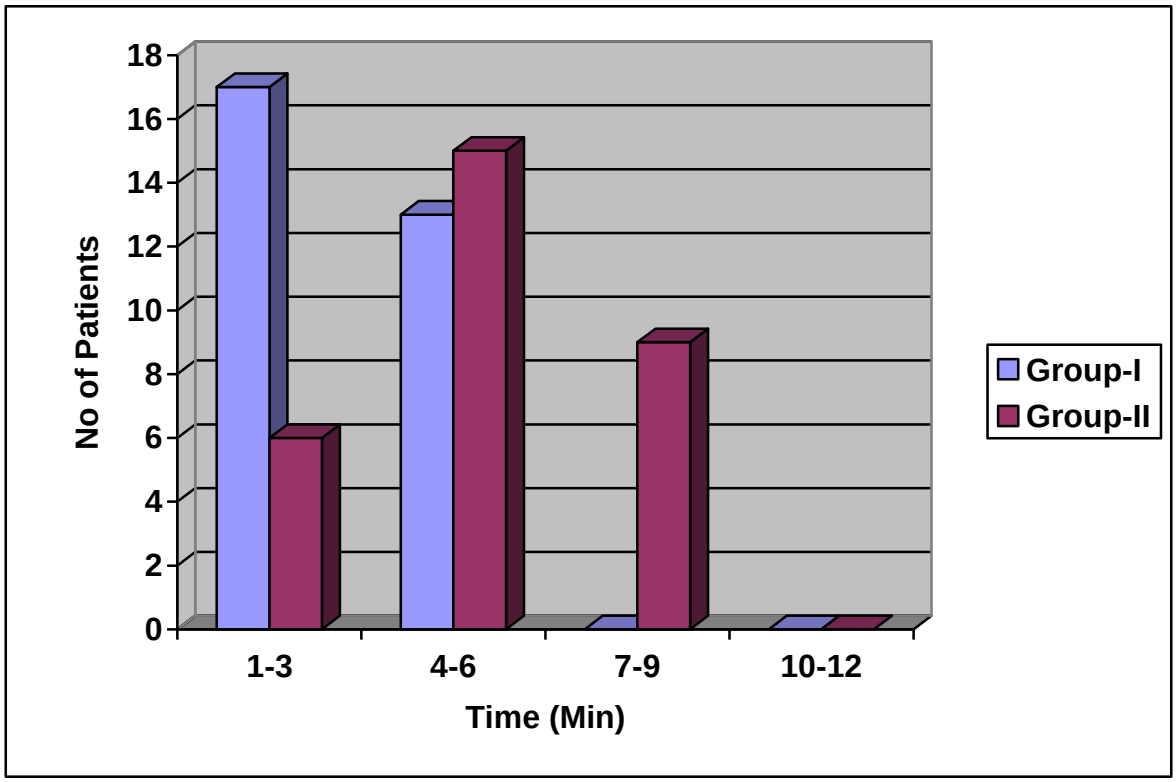


Table – 12 : Time Of Complete Blockade

Time (min)	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine
0 - 5	0	0
6 - 10	7	2
11 - 15	14	09
16 - 20	09	13
21 - 25	-	06
> 25	00	00
Range	10-20	10-25
Mean	14.6	17.73
SD	3.2	4.05
t	3.13	
P	<0.05	
Inference	H.S	

Time of complete blockade was 14.6 ± 3.2 in Group-I and 17.73 ± 4.05 in Group II. There was statistically significant difference in both the groups. So Group II had delayed blockade compared to Group –I.

Figure – 15 : Time of complete blockade

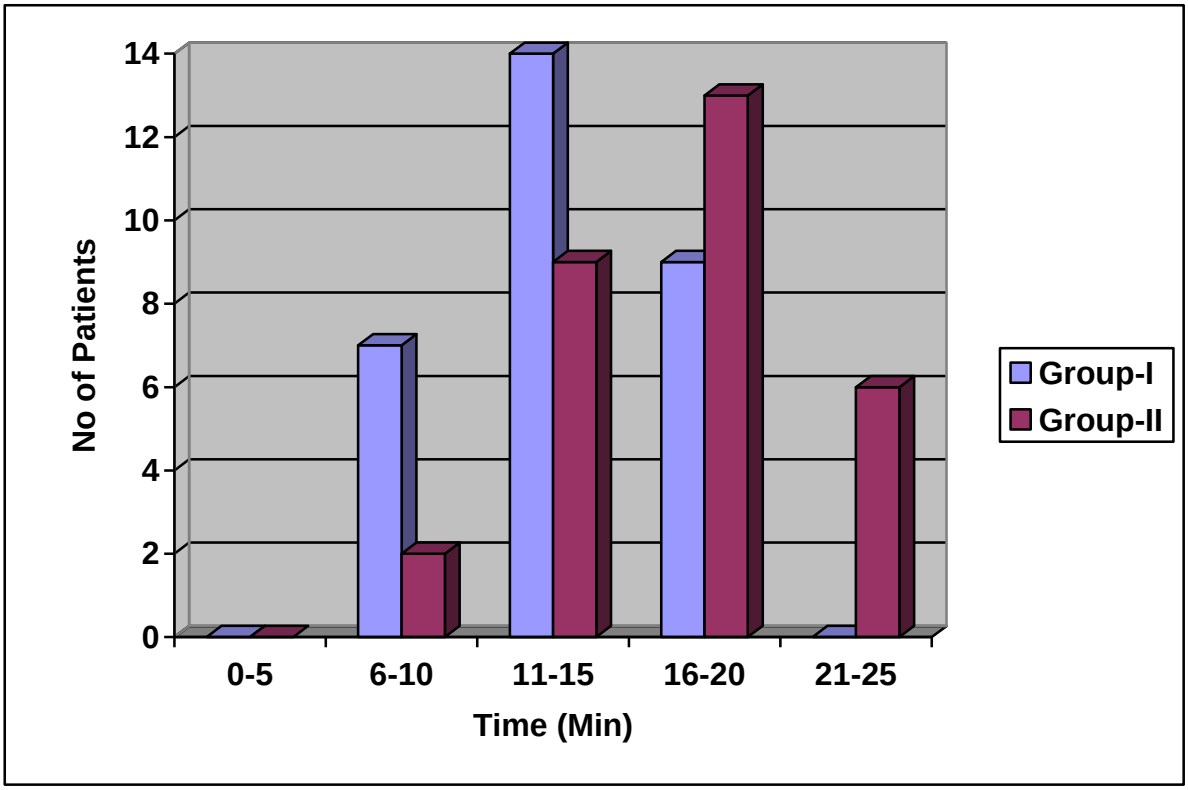


Table – 13 : Intra Operative Changes in Systolic Blood Pressure

	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine	't' value	'p' value	Inference
Pre-operative	125.20 ± 9.54	125.73 ± 7.80	0.24	>0.05	NS
After Pre-Medication	124.9 ± 9.24	124.86 ± 7.53	0.15	>0.05	NS
0 min	124.2 ± 9.51	125.2 ± 7.05	0.45	>0.05	NS
15 min	126.63 ± 7.09	124.66 ± 6.28	1.13	>0.05	NS
30 min	124 ± 6.32	121.53 ± 6.22	1.52	>0.05	NS
45 min	121.03 ± 6.64	119.69 ± 6.29	0.76	>0.05	NS
60 min	115.11 ± 7.07	115.0 ± 5.47	0.76	>0.05	NS
75 min	120.08 ± 6.64	119.8 ± 6.86	0.13	>0.05	NS
90 min	119.42 ± 6.63	119.71 ± 6.59	1.20	>0.05	NS
105 min	122.60 ± 6.74	120.93 ± 9.79	0.32	>0.05	NS
120 min	115.14 ± 7.64	116.0 ± 4.89	0.23	>0.05	NS
Post operative	118.4 ± 6.63	116.93 ± 6.11	0.89	>0.05	NS

Although a difference was noted in the systolic blood pressure in both the groups at various time periods, but on application of unpaired 't' test the difference was not found to be statistically significant.

Table – 14 : Intra Operative Changes In Diastolic Blood Pressure

Time	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine	't' value	'p' value	Inference
Pre-operative	78.66 ± 4.79	79.6 ± 3.53	0.85	>0.05	NS
After Pre-Medication	77.66 ± 4.30	79.0 ± 4.02	1.24	>0.05	NS
0 min	77.66 ± 4.32	78.33 ± 3.79	0.63	>0.05	NS
15 min	79.66 ± 1.82	78.53 ± 3.48	1.57	>0.05	NS
30 min	79.33 ± 2.53	78 ± 4.06	1.52	>0.05	NS
45 min	79.33 ± 2.53	78 ± 4.08	0.87	>0.05	NS
60 min	78.92 ± 3.14	78.07 ± 4.01	0.73	>0.05	NS
75 min	78.86 ± 3.60	78 ± 4.10	0.44	>0.05	NS
90 min	78.57 ± 3.58	78 ± 4.14	1.52	>0.05	NS
105 min	76.66 ± 5	76 ± 4.89	0.25	>0.05	NS
120 min	75.71 ± 5.34	76 ± 4.89	0.10	>0.05	NS
Post operative	78 ± 4.06	77.2 ± 4.47	0.72	>0.05	NS

Although a difference was noted in the diastolic blood pressure in both the groups at various time periods, but on application of unpaired 't' test the difference was not found to be statistically significant.

Table – 15 : Intraoperative Changes in Mean Arterial Pressure (In Mm Hg)

Time	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine	't' value	'p' value	Inference
Pre-operative	94.17 ± 5.62	94.98 ± 5.53	0.49	>0.05	NS
After Pre-Medication	93.41 ± 6.25	94.29 ± 5.17	0.114	>0.05	NS
0 min	93.17 ± 5.37	93.95 ± 4.30	0.136	>0.05	NS
15 min	95.32 ± 3.32	93.91 ± 4.48	0.24	>0.05	NS
30 min	94.22 ± 3.09	92.51 ± 4.86	0.341	>0.05	NS
45 min	90.98 ± 3.14	91.90 ± 4.79	0.139	>0.05	NS
60 min	92.60 ± 4.63	90.38 ± 4.01	0.352	>0.05	NS
75 min	92.19 ± 3.64	91.93 ± 4.59	4.59	>0.05	NS
90 min	93.23 ± 4.58	91.90 ± 4.11	0.277	>0.05	NS
105 min	91.97 ± 5.25	90.98 ± 5.89	0.110	>0.05	NS
120 min	88.85 ± 6.12	89.33 ± 4.89	0.105	>0.05	NS
Post operative	91.47 ± 4.79	90.44 ± 4.87	0.258	>0.05	NS

Although a difference was noted in the mean arterial pressure in both the groups at various time periods but on application of unpaired 't' test the difference was not found to be statistically significant.

Table – 16 : Intra Operative Changes In Pulse Rate

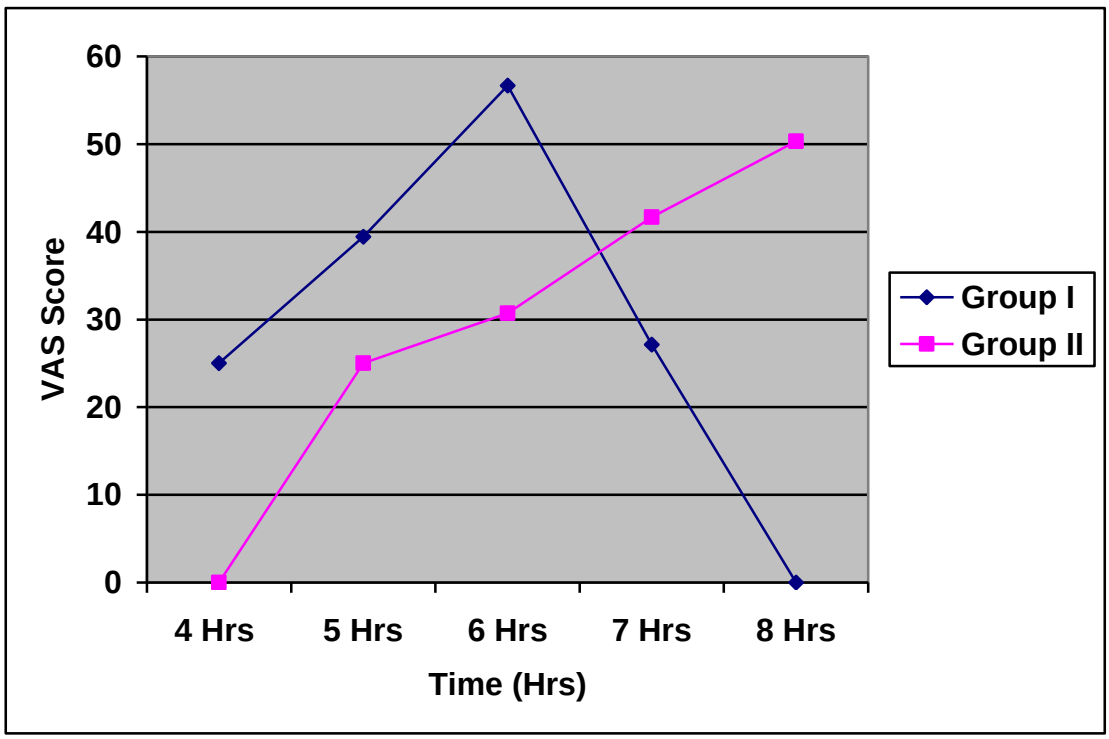
Time	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine	't' value	'p' value	Inference
Pre-operative	87.53 ± 7.48	87.22 ± 7.15	060	> 0.05	NS
After Pre-Medication	93.41 ± 5.53	94.28 ± 4.33	0.68	> 0.05	NS
0 min	93.17 ± 5.52	93.95 ± 4.35	0.60	> 0.05	NS
15 min	95.32 ± 3.10	93.91 ± 3.92	1.54	> 0.05	NS
30 min	94.22 ± 3.26	92.50 ± 4.45	1.69	> 0.05	NS
45 min	93.75 ± 3.22	92.30 ± 5.15	1.30	> 0.05	NS
60 min	86.76 ± 4.35	89.68 ± 5.84	0.970	> 0.05	NS
75 min	70.99 ± 7.30	71.28 ± 8.07	0.89	> 0.05	NS
90 min	74.53 ± 7.86	78.85 ± 6.75	0.30	> 0.05	NS
105 min	86.60 ± 6.09	85.58 ± 7.09	0.60	> 0.05	NS
120 min	84.35 ± 8.89	78.32 ± 6.40	0.89	> 0.05	NS
Post operative	91.46 ± 4.46	90.44 ± 4.42	0.89	> 0.05	NS

Although there was a difference in the mean pulse rate in both the groups at each time period but on publication of the unpaired 't' test the difference was not found to be statistically significant.

Table – 17 : Duration Of Analgesia (VAS Score)

VAS score	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine	t value	P value	Inference
Immediate post operative	0	0			
30 min	0	0			
60 min	0	0			
2 hrs.	0	0			
3 hrs.	0	0			
4 hrs.	25	0			
5 hrs.	39.44 ± 16.66	25 ± 0	2.30	0.03	HS
6 hrs.	56.66 ± 20.37	30.71 ± 9.75	2.10	0.0016	HS
7 hrs.	27.14 ± 8.09	41.66 ± 18.25	2.11	0.0299	HS
8 hrs.	-	50.35 ± 25.65			HS

Figure – 16 : Duration Of Analgesia (VAS Score)



At the end of 4 hours, Group I had visual analogue scale(VAS) of 25 which indicates mild pain, whereas in Group II patients had VAS score of 0 which indicates

no pain. Thus at the end of 4 hours, no requirement of rescue analgesia. The difference was statistically insignificant.

At the end of 5 hrs. Group I had VAS score of 39.44 ± 16.66, which indicates they required rescue analgesia, while in Group II had VAS score of 25 ± 0, indicates patient did not require rescue analgesia, as pain intensity was less.

While at the end of 6 hrs, Group I had VAS score of 56.66 ± 20.37, indicates moderate pain and analgesia required, and in Group II had VAS score of 30.71 ± 9.75, it did not required analgesia. The difference statistically significant.

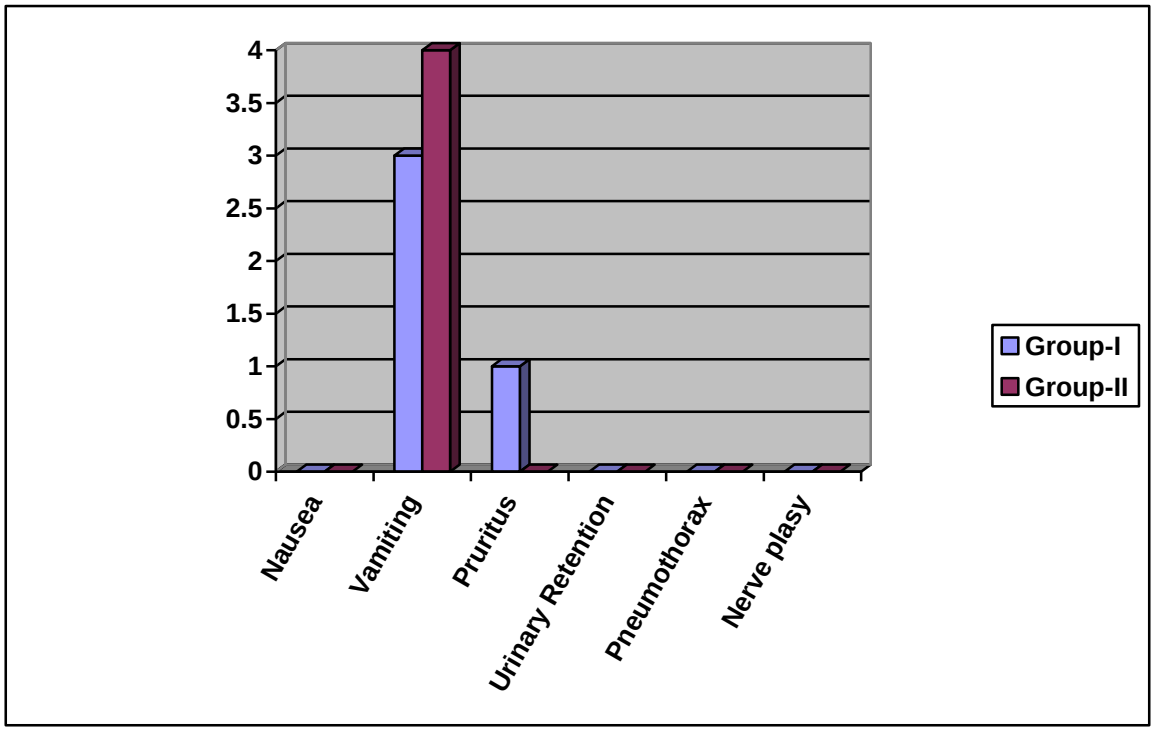
While at the end of 8 hrs, Group II had VAS score of 50 ± 25.65, thus they required rescue analgesia.

Thus, Group I patients require rescue analgesia at the end of 5 hrs while Group II patient require at the end of 8 hrs. Thus difference was statistically significant ($P < 0.05$). So Group II Buprenorphine patients had long duration of pain relief in post operative period.

Table – 18 :Complications

	Group-I (n=30) Butorphanol	Group-II (n=30) Buprenorphine
Nausea	0	0
Vomiting	3	4
Pruritus	1	0
Urinary retention	0	0
Pneumothorax	0	0
Nerve palsy	0	0

Figure - 17 : Complications



Only 3 patients in Group-I & 4 patients in Group-II had vomiting & difference was insignificant. Pruritus seen in one patient in Group-I. No other side effects were observed in any groups.

DISCUSSION

Presence of pain indicates presence of some disease or damage in the body. Cutting, tearing, stretching and burning of tissues during surgery produces intraoperative and post operative pain. Pain is maximum with orthopedic surgery. If this surgical pain is not treated adequately, it may lead to de-arrangement in various body functions. So treating pain is necessary to reduce the post operative morbidity and mortality.[39]

Peripheral nerve block given with Local anaesthetic drugs produce analgesia, but to prolong duration of post operative analgesia, many agents including variety of opioids have been used by various investigators. These include Morphine, Pethidine, Tramadol, Butorphanol and Buprenorphine.

Opioids produce analgesia when given in peripheral nerve blocks by following mechanisms. Primary afferent tissues (dorsal roots) have been found to contain opioid receptors. Opioids may diffuse from the brachial plexus sheath and then bind with opioid receptor at the dorsal horn.

The evidence of axonal flow of various macromolecules suggested possible centripetal axonal transport of opiods into the substantia gelatinosa after perineural injections.Peripheral nerve blocks are useful in patient where administration of general anaesthesia may be associated with increased risk of morbidity.

Brachial plexus block is accepted as mode of regional analgesia for upper limb surgeries. Supraclavicular blocks is a simple, easy to administer and economical technique. It produces dense analgesia and gives surgery of effective block. With this technique, landmarks are easy to locate and tourniquet pain is better tolerated.

SELECTION OF DRUG (OPIOID) VIA BRACHIAL PLEXUS ROUTE :

Different types of opioids drugs have been used in brachial plexus block for prolongation of analgesia.

(1) Kapral S, Gallmann G Waltl B,[40] have studied Tramadol in Local anaesthetic via axillary brachial plexus block and have demonstrated that 100 mg of Tramadol with Mepivacaine 1% provides prolongation of blockade without side effects.

(2) Z. Wajima et al,[11] have studied Inj. Butorphanol in Local anaesthetic via continuous brachial plexus block and have demonstrated that Butorphanol produces prolonged pain relief in post operative period without any side effects

(3) Viel and Colleagues,[10] have shown that Injection of Buprenorphine 3 μg/kg in supraclavicular brachial plexus blocks produces significantly longer pain relief than Morphine after upper limb surgery.

So here we have used Inj. Butorphanol (agonist at Kappa receptor and agonist antagonist at μ receptor) and Inj.Buprenorphine (agonist at Kappa receptor) in addition to Local anaesthetic drug via supraclavicular brachial plexus block.

As Butorphanol and Buprenorphine both are pure agonist Kappa receptor, it produces analgesia but as it is partial agonist antagonist at mu receptor, it has very negligible side effects like respiratory depression, nausea, vomiting, itching, euphoria, dependency etc.

DEMOGRAPHIC PROFILE:

In our study, a total of 60 patients belonging to age group 18-60 yrs were divided randomly into two groups (n=30). There were no differences between two groups with regard to demographic profile. Mean age in Group-I (Butorphanol) was 34.83 ± 11.58 and in Group-II (Buprenorphine) was 36.43 ± 14.86. Sex ratio was also comparable. In sex distribution 70% of patients in Group-I & 63.34% of patients in Group-II were male. This may be due to the fact that males are more prone to accidents & it was statistically insignificant. Mean weight was comparable in both the groups.

ONSET OF BLOCKADE:

Time to onset of motor blockade was 6.36 ± 1.15 min in Group I & 9.2 ± 1.32 min in Group-II & it was comparable in both the Groups.Time of onset of sensory blockade was 3.46 ± 1 min in Group-I and 5.23 ± 1.54 min in Group-II.Thus there was statistically difference between the onset of blockade. It shows that Buprenorphine group had delayed onset compared to Butorphanol Group.

As far as, time to complete blockade was 14.6 ± 3.2 (min) in Group-I and 17.73 ± 4.05 min in Group-II. There was statistically significant difference in both the Groups, $P < 0.05$. So Group II had delayed blockade compared to Group I.

CARDIOVASCULAR CHANGES :

(1) MEAN PULSE RATE :

The present study shows that pre operative pulse rate in Group-I and Group-II was 87.53 and 87.22 respectively.

Immediately postoperatively it was 91.46 in Group-2 and 90.44 in Group-II. On applying the unpaired 't' test the 't' value achieve was 0.89 for which P>0.05 hence the difference was non significant.

After premedication pulse rate in Group-I 93.41 and Group-II 94.28. The 't' value derived was 0.68 hence P>0.05 so result was non significant.

Intraoperatively, after induction, pulse rate in Group-1 and Group-II were 93.17 and 93.95 respectively. The 't' value derived was 0.60 hence P>0.05, so result was non significant.

After 15 min of induction, pulse rate in Group-I and Group-II were 95.32 and 93.91 respectively. The 't' value derived was 1.54 hence P >0.05. So result was not significant.

After 30 min, of pulse rate in Group-I and Group-II were 94.22 and 92.50 respectively. The 't' value derived 1.69 hence P>0.05 so result was non significant

After 45 min, pulse rate in Group-I and Group-II were 93.75 and 92.30 respectively. The 't' value derived was 1.30 hence P>0.05 so result was non significant

After 60 mins, pulse rate in Group-I and Group-II were 86.76 and 89.68 respectively. The 't' value derived 0.97 hence P>0.05, so result was non significant.

After 75 mins, pulse rate in Group-I and Group-II were 70.99 and 71.28 respectively. The 't' value derived was 0.89 hence P>0.05 so result was non significant.

After 90 mines, pulse rate ion Group-I and Group-II were 74.53 and 78.85 respectively. The 't' value derived was 0.30 hence P>0.05 so result was non significant.

After 105 mins, pulse rate in Group-I and Group-II were 86.60 and 85.58 respectively. The 't' value derived was0.60 hence P>0.05 so result was non significant.

After 50 mins, pulse rate in Group-I and Group-II were 84.35 and 78.32 respectively. The 't' value derived was 0.89 hence P>0.05 so result was non significant.

After post operatively pulse rate in Group-I and Group-II were 91.46 and 90.44 respectively. The 't' value derived was 0.89 hence P>0.05 so result was not significant.

Thus, although there was a difference in the mean pulse rate in both the groups at each time period but on publication of the unpaired 't' test the difference was not found to be statistically significant.

(2) MEAN ARTERIAL PRESSURE :

The present study showed that pre operative mean arterial pressure in Group-I and Group-II were 94.17 and 94.98 mm of Hg respectively.

After pre medication, it was 93.41 and 94.29 in Group-I and Group-II respectively. The 't' value derived was 0.114 hence P>0.05 so result was non significant.

At induction time mean arterial pressure in Group-I and Group-II were 93.17 and 93.95 respectively. The 't' value derived was 0.136 hence P>0.05, so result was non significant.

After 15 min, mean arterial pressure in Group-I and Group-II were 93.32 and 93.91 respectively. The 't' value derived 0.24 hence P>0.05, so result was non significant.

After 30 mins, mean arterial pressure in Group-1 and Group-II were 94.22 and 92.51 respectively. The 't' value derived was 0.341 hence P>0.05, so result was non significant.

After 15 min, mean arterial pressure in Group-1 and Group-II were 93.23 and 91.90 respectively. The 't' value derived was 0.139 hence P>0.05, so result was non significant.

After 60 mins, mean arterial pressure in Group-1 and Group-II were 90.98 and 90.38 respectively. The 't' value derived was 0.352 hence P>0.05, so result was non significant.

After 75 mins, mean arterial pressure in Group-1 and Group-II were 92.60 and 91.93 respectively. The 't' value derived was 0.343 hence P>0.05 so result were non significant.

After 90 mins, mean arterial pressure in Group-1 and Group-II were 92.19 and 91.90 respectively. The 't' value derived was 0.277 hence P>0.05 so result were non significant.

After 105 mins, mean arterial pressure in Group-1 and Group-II were 91.97 and 90.98 respectively. The 't' value derived was 0.110 hence P>0.05 so result were non significant.

After 120 mins, mean arterial pressure in Group-1 and Group-II were 88.85 and 89.33 respectively. The 't' value derived was 0.105 hence P>0.05 so result were non significant.

Post operatively, mean arterial pressure in Group-I and Group-II were 91.47 and 90.44 respectively. The 't' value derived was 0.258 hence P>0.05 so result was non significant.

Thus, although a difference was noted in the mean arterial pressure in both the groups at various time periods but on application of unpaired 't' test the difference was not found to be statistically significant.

VISUAL ANALOGUE SCALE SCORE :

Post operatively comparison of duration of post operative analgesia was done by visual analogue scale score. As shown in the Graph, at the end of 3 hours, none of the patients from both the group experience pain. However at the end of 5 hrs all the patients in Group-I had pain with intensity of 39.44 ± 16.66 on VAS score,Thus Group-I patients required rescue analgesia at the end of 5 hrs, where as Group-II patients had VAS score of 25 ± 0 but it was less and patients did not ask for analgesia, rescue analgesics were not given to the patients.

While at the end of 6 hrs, Group I had VAS score of 56.66 ± 20.37, indicates moderate pain and analgesia required, and in Group II had VAS score of 30.71 ± 9.75, it did not required analgesia. But at the end of 8 hours, Group-II patients had pain intensity of 50.35 ± 25 on VAS score, so all the patients were given rescue analgesia.The Group-I patients required rescue analgesia at the end of 5 hrs while Group-II patients required at the end of 8 hrs. Thus Buprenorphine produces statistically significant prolonged duration of post operative analgesia.

Our study is comparable with the study of Viel and colleagues.[10] They have studied comparison of Buprenorphine and Morphine in supraclavicular brachial plexus block and evaluated that Buprenorphine significantly produces prolonged postoperative pain relief.

Our study is also comparable with the study of Z Wajima et al.[12] They have studied comparison of continuous brachial plexus infusion of Butorphanol (B), Mepivacaine (M) and Mepivacaine Butorphanol (MB) mixture for postoperative analgesia and evaluated that MB mixture prolongs the duration of post op analgesia.

POST OPERATIVE COMPLICATIONS :

In our study, 3 patients from Group-I and 4 patients from Group-II had vomiting but the difference was statistically insignificant (P>0.05). Our results are comparable to those of Viel EJ, Eledjan JJ and Z. Wajima, Y. Nakajima et al. They also reported vomiting in their patients and reported that Brachial plexus infusion of opioids had more potent analgesic effect than systemic administration. So lower dose of opioids into neurovascular sheath rather than systemic administration should be chosen to prevent side effects such as nausea and vomiting.

CONCLUSION

- In Group II (Buprenorphine), onset of sensory, motor blockade and complete blockade was delayed as compared to Group I (Butorphanol).

- And duration of postoperative analgesia was longer (upto 8-9 hrs postoperatively) in Group II, compared to Group I had postoperative analgesia duration of 5-6 hrs.

So we concluded that both opioids are potent postoperative analgesics in brachial plexus block, but Buprenorphine is more potent and produces longer duration of postoperative analgesia than Butorphanol.

SUMMARY

This study entitled "A Comparative study of Butorphanol v/s Buprenorphine in supraclavicular brachial plexus block for postoperative analgesia" was conducted in 60 patients of either sex, belonging to 18-60 yrs of age, ASA grade I and II admitted for orthopedic Upper limb surgeries in the department of anesthesiology, B.L.D.E.A.'s Shri B. M. Patil Medical College, Hospital and Research center, Bijapur from Dec 2007 to Jan 2009.

All the patients were divided into two groups :

Group I: Bupivacaine plain 0.5% (2 mg/kg)
Lignocaine plain 2% (4 mg/kg)
Butorphanol 1 mg.

Group II: Bupivacaine plain 0.5% (2 mg/kg)
Lignocaine plain 2% (4 mg/kg)
Buprenorphine 100 μgm

Demographic variables: such as age, male and female ratio, weight and type of surgery were comparable in both groups.

Onset of blockade: Duration of sensory as well as motor and also complete blockade were comparable in both groups which shows that Group II Buprenorphine had delayed onset compared to Group I Butorphanol .

Cardio vascular changes: In our study preoperative, intraoperative and post operative pulse rate and blood pressure did not reveal any statistically significant difference in both the groups.

Quality of Analgesia: In Group I patients, VAS score was 39.44 ± 16.66 at the end of 5 hours while in Group II patients 50.35 ± 25.65 VAS score at the end of 8 hours. So the duration of analgesia was upto 5-6 hours in Group I, where it was upto 8-9 hours in Group II.

Side Effects: Three patients from Group I and four patients from Group II had vomiting. No other complications and side effects were encountered in our study.

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ANNEXURE – I

PROFORMA FOR EVALUATION OF POST – OPERATIVE ANALGESIA

Sl no. :

Name :

Age :

Sex :

I.p.no. :

Weight :

Date :

Diagnosis :

Operation perfomed :

PRE – OPERATIVE EXAMINATION:

General physical examination:

BUILT : Obese/ moderate/ thin

PALLOR : ICTERUS : CLUBBING :

CYANOSIS : OEDEMA :

PR : bpm

BP : mm of Hg

SPINE : normal / kyphosis / scoliosis / local infection

Airway assessment:

MOUTH OPENING :

MALLAMPATI GRADE :

CERVICAL SPINE MOVEMENT :

TMJ MOVEMENT :

SHORT NECK / BUILDING :

Systemic examination:

R.S :

CVS :

OTHER:

Investigations:

Hb %	:	Blood sugar	:	Urine analysis:
ECG	:	Bleeding time	:	Clotting time:
B. urea	:	S. creatinine	:	Others :

ASA GRADE:

PREMEDICATION:

Inj. Glycopyrrolate 0.2mg and Inj. Ondansetron 4mg I.V given five minutes before procedure.

PROCEDURE	:	Supraclavicular Brachial Plexus Block
GROUP I	:	Inj. Butorphanol 1mg
		Inj. Lignocaini (2%, 4mg /kg)
		Inj. Bupivacaine (0.5%, 2mg/ kg)
GROUP II	:	Inj. Buprenorphine 100mg
		Added to local anaesthetic mixure.

TIME ADMINISTRATION:

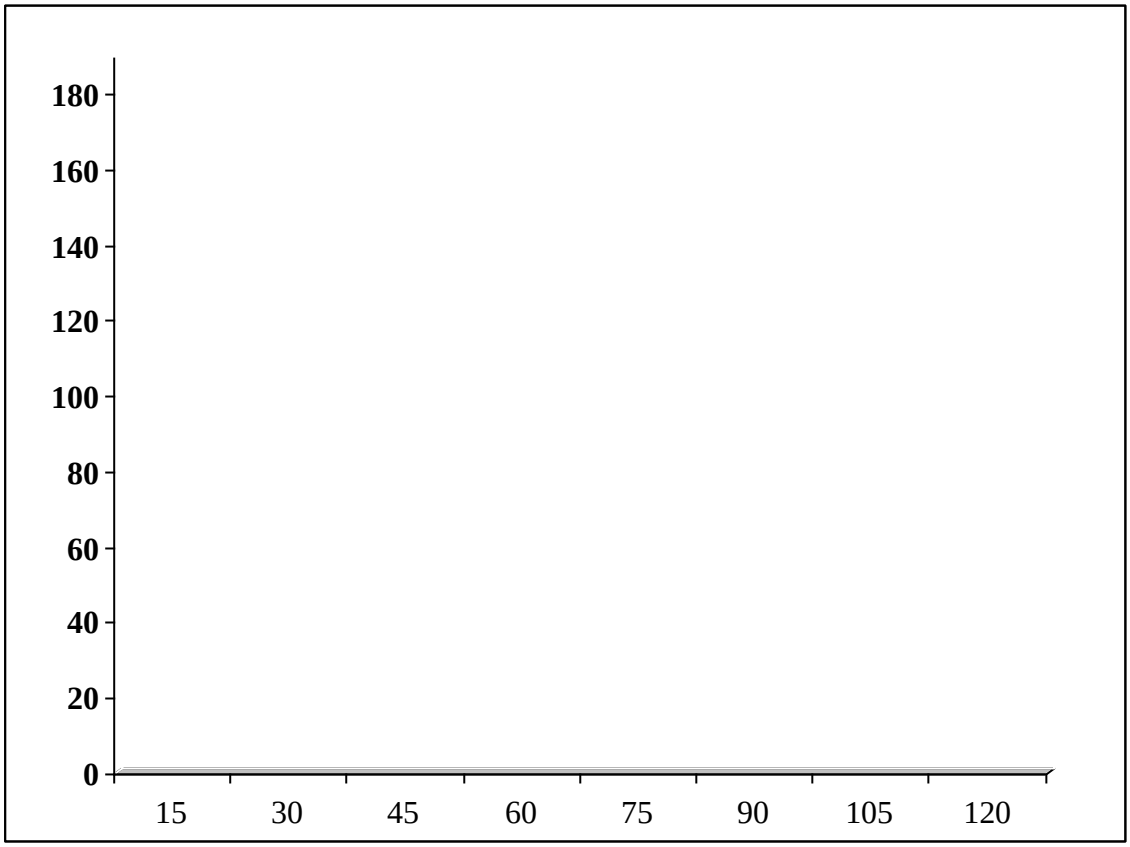
ONSET OF BLOCKADE:

Sensory:

Motor:

Complete block:

INTRA OPERATIVE VITALS



COMPLICATIONS:

Nausea : Yes / No

Vomiting : Yes / No

Pruritus : Yes / No

Urinary Retention : Yes / No

Pneumothorax : Yes / No

Convulsions : Yes / No

Hypotension : Yes / No

POST – OPERATIVE OBSERVATION

TIME	PR	BP	VAS	VARS
Immediate post operative				
30 Min				
1 hr				
2 hr				
3 hr				
4 hr				
5 hr				
6 hr				
7 hr				
8 hr				
9 hr				

ANNEXURE II

SAMPLE INFORMED CONSENT FORM

Title of Project : **"COMPARATIVE STUDY OF BUTORPHANOL V/S BUPRENORPHINEINSUPRACLAVICULAR BRACHIALPLEXUS BLOCK FOR POSTOPERATIVE ANALGESIA"**

Guide **: Dr D. G. Talikoti**

P.G. Student **: Dr. Vinod CN**

Purpose of research :

I have been informed that this study will comparatively evaluate postoperative analgesia between butorphanol and buprenorphine in supraclavicular brachialplexus block in patients undergoing upper limb orthopedics surgeries.

Procedure:

I understand that I will be given either butorphanol or buprenorphine in supraclavicular brachialplexus block for comparison of duration of post operative analgesia.

Risks and discomforts

I understand that I may experience some pain, discomforts and cardiovascular effects during procedure. This is mainly the result of my condition and procedures of this study are not expected to exaggerate these feelings, which are associated with the usual course of procedure.

Benefits:I understand that my participation in this study will help in finding out the efficacy of butorphanol and buprenorphine in supraclavicular brachialplexus block for postoperative analgesia.

CONFIDENTIALITY:

I understand the medical information produced by this study will become part of my hospital record and will be subject to the confidentiality. Information of sensitive and personal nature will not be part of the medical record, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers, such as photographs will be used only with my special written permission. I understand that I may see the photographs before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. Vinod CN at the department of Anaesthesiology is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Vinod CN may terminate my participation in this study at any time after he has explained the reasons for doing so.

ANNEXURE III

INJURY STATEMENT

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly then appropriate treatment would be available to me. But no further compensation would be provided by the hospital. I understand that by my agreement to participate in this study and not waiving any of my legal rights.

I have explained to _____ the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability.

_____ _____

Investigator Date

I confirm that Dr. Vinod CN has explained to me the purpose of the research, the study procedure that I will undergo and the possible risks and discomforts as well as benefits that I may experience in my own language. I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project

_____ _____

Participant Date

_____ _____

Witness to signature Date

Group II Buprenorphine

Sl NO	Name	Age	Sex	Wt.	IP No.	Operation	Pre op		After premedication		Onset of Blockade		0 min		15 min		30 min		45 min	
							PR	BP	PR	BP	Sensory	Motor	PR	BP	PR	BP	PR	BP	PR	BP
1	Bhimarao	24	M	55	467	ORIF	72	130/90	80	130/80	4	8	80	130/80	88	130/80	88	126/80	84	126/80
2	Dineshbhai	40	M	65	820	Ulna platting	80	130/80	84	130/80	5	10	84	130/80	88	130/80	88	126/80	84	126/80
3	Vishal	19	M	45	725	Excision	88	120/76	92	120/70	7	10	92	120/70	92	120/80	88	120/80	88	120/80
4	Bharathi	50	F	65	2308	ORIF	80	140/80	88	141/80	7	10	88	140/80	88	140/80	84	136/80	84	136/80
5	Subhashani	25	F	55	1080	ORIF	84	120/80	88	120/80	8	12	88	120/80	92	1269/80	88	126/80	84	120/80
6	Bapurayya	38	M	60	1621	Platting	76	130/86	80	130/80	7	10	80	130/80	92	130/80	88	136/80	88	130/80
7	Savitaben	40	F	50	2854	ORIF	88	120/80	88	120/80	6	10	88	120/80	88	126/80	84	126/80	84	120/80
8	Gopal	25	M	55	1307	Implant removal	80	130/76	84	130/80	7	12	84	130/80	88	126/80	88	126/80	84	126/80
9	Bharatgouda	18	M	60	1963	Platting	76	120/80	84	120/80	5	9	84	120/80	84	120/80	80	116/80	80	110/80
10	Rahul	18	M	50	2609	Platting	96	120/70	100	120/70	5	8	100	120/70	96	120/80	96	116/70	96	1169/70
11	Kasamali	44	M	55	3176	Implant Removal	72	110/76	80	110/70	5	9	80	110/70	88	120/80	88	120/80	84	1169/80
12	Lakshmawwa	50	F	55	3241	ORIF	76	136/80	84	130/80	7	10	84	130/80	88	130/80	84	126/80	84	126/80
13	Yusubhai	30	M	60	3780	ORIF	88	130/80	92	130/80	7	10	92	130/80	92	130/80	92	126/80	88	126/80
14	Hasanamma	45	F	60	3871	ORIF	80	140/86	88	140/80	5	8	88	140/80	92	140/80	92	136/80	88	130/80
15	Mubarakhbai	35	M	60	4008	Bone grafting	80	120/80	84	120/80	5	10	84	120/80	88	126/80	84	120/80	84	120/80
16	Guru	19	M	55	4619	ORIF	76	130/80	80	130/80	3	7	80	130/80	88	130/80	88	126/80	84	126/80
17	Siddhraji	25	M	50	4972	Platting	76	120/80	80	120/80	7	10	80	120/80	88	120/80	88	120/80	84	116/80
18	Ramiben	50	F	50	4599	ORIF	80	140/80	84	140/80	4	10	84	140/80	88	140/80	88	126/80	84	136/80
19	Chandrika	35	F	55	5421	TBW	88	130/80	88	130/80	5	7	88	130/80	92	126/80	88	120/80	84	120/80
20	Rajugouda	18	M	50	5612	K wiring + CR	88	110/70	92	110/70	3	8	92	110/70	92	120/80	88	120/80	88	120/80
21	Riaaz	19	M	55	6093	ORIF	88	130/80	88	130/80	7	10	88	130/80	92	130/80	92	126/80	88	126/80
22	Poonam	44	F	50	7109	ORIF	88	120/80	88	120/80	3	8	88	120/80	88	120/80	84	120/80	84	120/80
23	Premji	30	M	45	7214	ORIF	80	110/70	84	110/70	6	10	84	110/70	88	120/80	88	120/80	84	116/80
24	Jayaraj	22	M	50	7299	ORIF	96	110/70	100	110/70	3	8	100	110/70	100	120/80	96	120/80	84	116/80
25	Ratnawwa	47	F	50	8604	ORIF	88	120/80	92	120/80	4	7	92	120/80	92	120/80	88	116/80	96	110/80
26	Neelkanth	30	M	65	8742	ORIF	80	130/80	84	130/80	5	10	84	130/80	88	130/80	84	126/80	84	126/80
27	Jayalaksmi	50	F	55	9871	ORIF	76	130/80	84	130/80	3	8	84	Oct-80	88	130/80	88	126/80	84	126/80
28	Tukkapa	50	M	60	9453	ORIF	80	140/80	88	136/80	5	9	88	136/80	92	136/80	88	136/80	84	130/80
29	Ahmed	30	M	55	9860	ORIF	80	130/80	88	130/80	6	10	88	130/80	88	130/80	84	126/80	84	126/80
30	Manjuben	45	F	55	11087	Repair	88	110/70	92	110/70	3	8	92	110/70	88	110/70	88	110/70	84	110/70

60 min		75 min		90 min		105 min		120 min		POst op		VAS Score										Complication
PR	**BP**	**PR**	**BP**	**PR**	**BP**	**PR**	**BP**	**PR**	**BP**	**PR**	**BP**	**Post Op. immediate**	**30 min**	**60 min**	**2 hr.**	**3 hr**	**4 hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**	**9 hr**	
84	126/80	84	120/80	84	120/80					84	120/80	0	0	0	0	0	0			45			
84	126/80	80	126/80	80	126/80					80	120/80								25				
88	120/80									84	120/80									25			
84	136/80	80	130/80	80	130/80	80	130/80	80	130/80	80	130/80								45				
84	120/80	80	120/84	80	120/80					80	120/80								25				
88	130/80	84	130/80	84	130/80					84	130/80								25				
80	120/80	80	120/80	80	120/80	84	116/80	84	116/80	84	116/80									45			Vomiting
84	126/80	84	130/80	84	130/80					80	130/80							25					
80	116/80	80	120/80	80	120/80					80	120/80									25			Vomiting
92	110/70	92	110/70	92	110/70					92	110/70									45			
80	116/80	80	110/80	84	110/80	84	110/80			84	110/80										45		
80	120/80	80	120/80		126/80					80	120/80										25		
88	120/80	84	126/80	84	120/80					84	126/80										25		
88	126/80	84	120/80	84						84	120/80									45			
84	120/80				116/80					84	120/80									25			
84	120/80	80	120/80	80	110/70	84	110/70	84	110/70	584	110/70										25		
84	119/80	80	110/70	80	120/80	80	110/70	80	110/70	80	110/70								25				
84	130/80	84	120/80	84						84	120/80									75			
										84	120/80									75			
					120/80					88	120/80									45			
88	126/80	84	120/80	84		84	110/80	80	110/80	80	110/80							25					Vomiting
80	120/80				110/70					80	120/80								25				
84	110/80	84	110/70	84	110/80	80	110/70	80	110/70	80	110/70										25		
92	116/80	92	110/80	92						92	110/80										45		
80	110/70				120/80					80	110/70										25		
84	126/80	80	120/80	80	120/80	80	120/80	80	120/80	80	120/80								45				
84	120/80	80	120/80	80						80	120/80									25			Vomiting
80	130/80	80	130/80		120/80					80	130/80										25		
80	120/80	80	120/80	76		76	120/80			76	120/80									25			
84	110/70									84	110/70										25		