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Ultrasound Guided Transversus Abdominis Plane Block and Nalbuphine and Ketamine as Adjuvants for Abdominal Hysterectomy

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ABSTRACT

Background: The transverse abdominis plane (TAP) block is a regional block anesthetizing the nerves covering the lower abdominal wall. The TAP block can be used for postoperative analgesia management in open and laparoscopic abdominal surgeries.

Aim: To review transversus abdominis plane block for abdominal hysterectomy, including the anatomy, ultrasound-guided approaches, complications, and the pharmacology of ketamine and nalbuphine as adjuvants to local anesthetics.

Conclusion: Ultrasound guidance allows direct visualization of the abdominal wall muscular layers and the needle during TAP block. Adjuvants to local anesthetics are used to prolong the duration of sensory-motor block and to limit cumulative local anesthetic requirements.

Keywords: Transversus abdominis plane block; abdominal hysterectomy; ultrasound guidance; ketamine; nalbuphine; bupivacaine.

INTRODUCTION

The transverse abdominis plane (TAP) block is a regional block anesthetizing the nerves (T10 to L1) hence covering the lower abdominal wall. Post-laparoscopic hysterectomy pain has two components: somatic and visceral. Somatic pain has two subdivisions, cutaneous and deep, Cutaneous pain originates from nociceptors within the abdominal wall and is transmitted via T10-L1 spinal nerves running laterally in the abdominal wall in between transverse abdominis and internal oblique muscle layers. Visceral uterine nociceptive pain is transmitted via the afferent nerve stimuli ascending through the inferior hypogastric plexus which enters the spinal cord (T10-L1 nerves) [(1)].

The TAP block can be used for postoperative analgesia management in open and laparoscopic abdominal surgeries and inpatient and outpatient surgical procedures. Unilateral left- or right-sided blocks are used for unilateral surgical procedures, such as cholecystectomy, appendectomy, nephrectomy, or renal transplants. In contrast, bilateral TAP blocks are used for midline and transverse abdominal incisions, such as umbilical or ventral hernia repair, cesarean deliveries, hysterectomy, and prostatectomy. TAP blocks are part of multimodal pain management for abdominal surgeries, which adds analgesic benefit to patients, reducing postoperative opioid requirements. TAP blocks are typically placed intraoperatively, either before the surgical incision or at the end of the procedure before emergence from anesthesia. The TAP block's efficacy depends on the spread of LA across the interfacial plane. Newer tissue plane blocks, like the quadratus lumborum block, provide somatic and visceral analgesia. [(2)]

INDICATIONS AND ANATOMICAL CONSIDERATIONS

Providing analgesia after an abdominal wall procedure in various abdominal surgeries is an indication of the TAP block. The TAP block can be performed for open abdominal surgeries and laparoscopic procedures. The block is an easier and less risky substitute for epidural anesthesia in postoperative pain control for abdominal surgeries. [3]

Bilateral blocks are used for midline and transverse abdominal incisions, such as ventral hernia repair, umbilical hernia repair, exploratory laparotomy, colostomy closure, cesarean delivery, hysterectomy, radical retropubic prostatectomy, bariatric surgery, inguinal hernia repair, and laparoscopic surgery.

TAP blocks can also play a role in chronic pain management. [4]

The anterior abdominal wall confines abdominal viscera, stretches to accommodate accommod the expanding uterus, and provides surgical access to the internal reproductive organs [5]

The abdominal wall is a layered structure, consisting of skin, subcutaneous fat, fascia, muscle layer, transversalis fascia and the peritoneum [6]

The anterior abdominal wall contains five pairs of muscles that mainly attached above and laterally to the sternum and lower ribs and below to the pelvic bone. Three of the muscles are located laterally and superimposed as sheets one on the other from superficial to deep; they are the external oblique, the internal oblique, and the transverses muscles. The rectus and pyramidalis muscles make up the medial group lying adjacent to the linea alba and enclosed in varying degrees by the rectus sheath [7]

The fibrous aponeuroses of the external oblique, internal oblique, and transverses abdominis muscles join in the midline to create the rectus sheath. The construction of this sheath varies above and below a demarcation line, termed the arcuate line. Cephalad to this line, the aponeuroses invest the rectus abdominis bellies above and below. Caudal to this line, all aponeuroses lie anterior to the rectus abdominis muscle, and only the thin transversalis fascia and peritoneum lie beneath [5].

Each of the three flat muscles is covered on its anterior and posterior surfaces by a layer of investing abdominal fascia. In general, these layers are unremarkable except for the layer deep to the transversus abdominis muscle "the transversalis fascia", which is better developed [8]

The skin, muscles and parietal peritoneum of the anterior abdominal wall are innervated by the lower six thoracic nerves (T6-T12) and the first lumbar nerve (L1)

Along their course, T7-T12 and L1 supply branches to the anterolateral abdominal wall muscles. All terminate by supplying skin: Nerves T7 to T9 supply the skin from the xiphoid process to just above the umbilicus. T10 supplies the skin around the umbilicus. T11, T12, and L1 supply the skin from just below the umbilicus to, and including, the pubic region [5].

The ilioinguinal nerve arises from the first lumbar nerve and emerges from the lateral border of the psoas major just below the iliohypogastric nerve, passes obliquely across the quadrates lumborum and iliacus, perforates the transverse muscle above the iliac crest, and communicates with the iliohypogastric nerve between the transverse and internal oblique muscles (Manolakos et al., 2024).

TECHNIQUES OF TRANSVERSUS ABDOMINIS PLANE BLOCK

There are several TAP block techniques based on how the TAP block compartment is identified:

The original landmark-guided TAP block at the level of the (Petit) triangle) is situated between the iliac crest and subcostal margin. The base of the triangle is formed by the iliac crest, and it is bounded anteriorly by the external oblique muscle and posteriorly by the latissimus dorsi muscle.

The US-guided TAP block that can be found anatomically in the subcostal, lateral, and posterior approach

The laparoscopic-guided TAP block involves visualizing from inside the abdominal cavity and sensing 2 "pops" or loss of resistance with the needle from outside the abdomen during surgery.

The US-guided technique is considered the gold standard in TAP blocks because it is easy for the operator to acquire US images and safe for the patient to have the procedure performed under direct visualization of the needle prior to the injection of LA. For these techniques, the patient should be positioned supine, except for slight lateralization for the posterior approach in some cases. A high-frequency linear or curvilinear US transducer should be placed in the abdomen with gel for adequate contact and transmission of the US waves. [9]

The skin and subcutaneous fat are the most superficial layers in the visualized US image. There are 3 muscular layers, from superficial to deep: the external oblique, followed by the internal oblique (IO), and lastly, the transversus abdominis (TA) muscle. The IO muscle is usually the thickest muscle layer in most patients, while the TA muscle is the thinnest. If the layer borders are uncertain, increase the ultrasound's depth to confirm the bowel beneath the Transversus abdomins muscle. Scanning posteriorly, the IO and Transversus abdomins muscles show the 2 layers come together to form the thoracolumbar fascia. Scanning medially, the aponeurosis of the 3 muscle layers comes together to form the rectus sheath. Upon identifying the TAP compartment with the US probe, infiltrate the patient's skin using lidocaine (if the patient is awake) and penetrate the skin with the block needle using an in-plane technique, making sure to visualize the needle tip on US throughout its entire trajectory. Upon entering the plane between the IO and the Transversus abdomins muscles, the LA is slowly injected after negative aspiration of blood. The TAP compartment will begin to separate, hydrodissect, or "unzip" as the LA is injected, pushing the Transversus abdomins muscle down. Usually, an injection of 15 mL to 20 mL of LA is recommended for each side of an adult patient. The dose and volume depend on the patient's weight as well as the concentration of the LA. The spread of LA along the TAP compartment is responsible for the success of the block. Studies have shown that the efficacy of the block is improved when injecting 15 mL or more. [10]

There are 3 approaches for US-guided TAP block to target the compartment anatomically:

Subcostal approach: Targets the TAP compartment in the anterior abdominal wall beneath the costal margin. The high-frequency probe should be located in the lower margin of the rib cage between the xiphoid process and the anterosuperior iliac spine at the level of the anterior axillary line. The objective is to deposit the LA in the plane between the Transversus abdomins muscle and the posterior rectus sheath. The needle should be inserted above the rectus abdominis muscle and advanced until it is positioned between the anterior edge of the Transversus abdomins muscle and the posterior rectus sheath. [11] this area is covered by T6 to T9 dermatomes, blocking the anterior cutaneous nerves. The anterior approach provides analgesia for open or laparoscopic cholecystectomy surgeries.

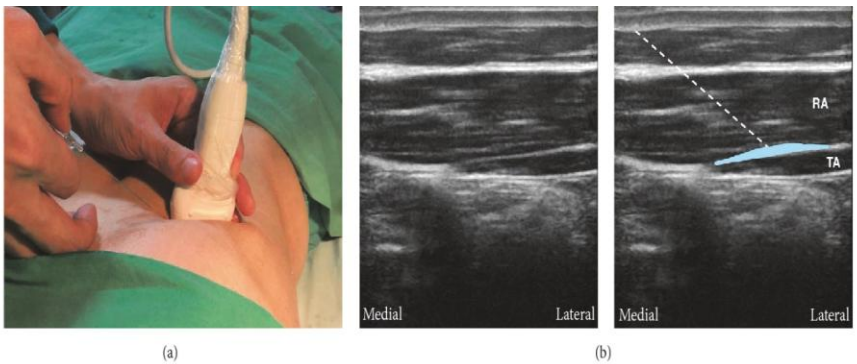


Fig. 1: Subcostal approach of transversus abdominis plane (TAP) block [12]

Lateral approach: Targets the TAP compartment in the lateral abdominal wall. The high-frequency probe should be located in the midaxillary line between the bony prominences of the subcostal margin and the iliac

crest. The 3 muscular layers in the abdominal wall should be visualized. The objective is to deposit the LA in the plane between the Transversus abdomins and IO muscles. The needle should be inserted and advanced until it reaches the TAP plane. This area is covered by T10 to T12 dermatomes, blocking the anterior cutaneous nerves. The lateral approach provides analgesia for most abdominal surgeries, including laparoscopic surgery, open appendectomy, ventral hernia repair, umbilical hernia repair, exploratory laparotomy, colostomy closure, cesarean delivery, hysterectomy, bariatric surgery, radical retropubic prostatectomy among others. [13]

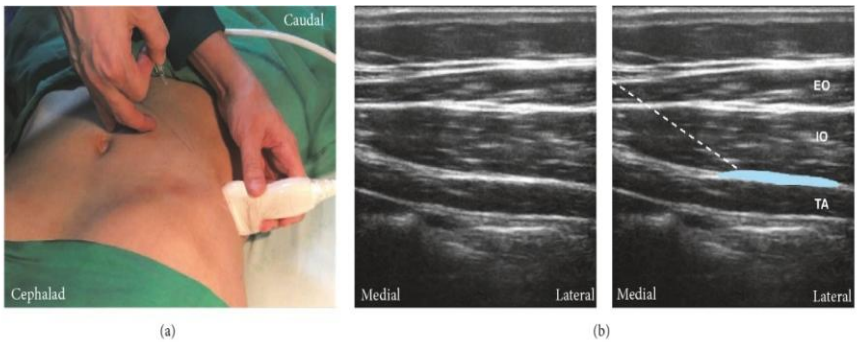


Fig. 2 : Lateral approach of transversus abdominis plane (TAP) block [2]

Posterior approach: Targets the TAP compartment at the level of the lumbar triangle of Petit or the anterolateral aspect of the quadratus lumborum muscle. The high-frequency probe should be located in the midaxillary line and then displaced lateral and posteriorly to the end limit of the 3 muscular layers. The objective is to deposit the LA in the plane among the Transversus abdomins muscle and the IO muscle but in the posterior end limit of the TAP plane. The needle should be inserted in the midaxillary line and advanced posteriorly until it reaches the TAP plane. This area is covered by T9 to T12 dermatomes, blocking the anterior and lateral cutaneous nerves. The posterior approach provides analgesia for nephrectomies, renal transplants, and others. [2]

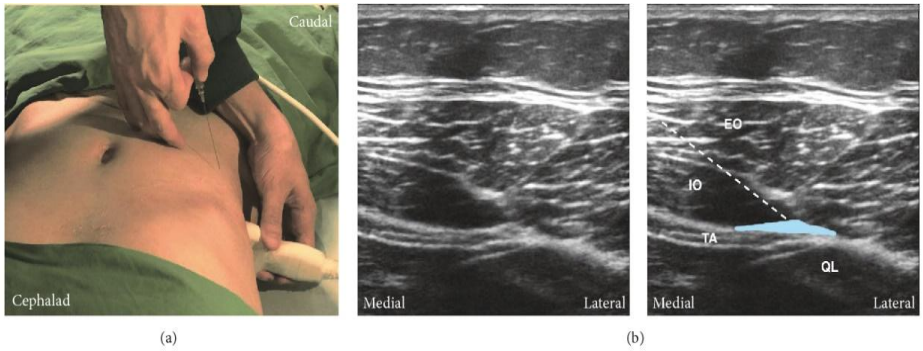


Fig.3 : Posterior approach of transversus abdominis plane (TAP) block(Tsai et al., 2017) [2]

COMPLICATIONS AND SAFETY

Complications related to TAP blocks are rare. Some complications reported in the literature include:

Utilizing US guidance rather than anatomical landmarks is recommended to increase the success rate and minimize these complications. There have been minimal reported complications after the universal implementation of the US-guided technique for the TAP block. [14]

Neurological injury is rare in TAP blocks because these are field blocks, relying on the high volume of the LA injected to facilitate adequate blockade of the nerves in the compartment rather than targeting a specific nerve. If a neurologic injury occurs, it might be from direct nerve trauma from the needle, hematoma, or local infection. Excessive needle insertion, especially in thin, older, or deconditioned patients, may also lead to complications such as visceral trauma, vascular injury, intraperitoneal injection, or intrahepatic injection. [15]

Case reports have also described transient femoral nerve palsy when some LA injected for the TAP block could trail on the fascia iliaca below the inguinal ligament, producing an inadvertent blockage of the femoral nerve. If this incident happens, the surgical team should be made aware, and the patient has to be advised regarding the potential risk of falls. LA injection within the TAP block is within an interfascial plane that is well vascularized; the reason why the operator should perform careful aspiration before injecting a LA is to avoid an accidental vascular puncture and intravascular injection that might lead to LA systemic toxicity (LAST) which is a rare but known complication of the TAP block. [16]

KETAMINE PHARMACOLOGY

General Properties and Mechanism of Action

Ketamine has been used as an anesthetic drug for over 65 years [17]. An enantiomeric, lipid-soluble phencyclidine derivative, ketamine is one of the most commonly used drugs in anesthesia. As a nonselective NMDA receptor antagonist, it has equal affinity for different NMDA receptor types. NMDA is a subgroup of ionotropic glutamate receptors, along with AMPA and kainite. Ketamine is inexpensive and therefore widely used in developing countries. It additionally has particular utility for anesthesia induction in hemodynamically unstable patients.

Ketamine administration has long been known to mediate a wide variety of pharmacological effects, including dissociation, analgesia, sedation, and bronchodilation. Though ketamine is known most widely for its anesthetic properties, recent research has uncovered multiple novel uses for this drug, including neuroprotection, combatting inflammation and tumors, and treatment of depression, seizures, chronic pain, and headache. Racemic ketamine, a mixture of (S)- and (R)-ketamine is commonly used in this research, though both (S)-ketamine and (R)-ketamine alone are also subjects of study. While (S)-ketamine carries roughly 3- to 4-fold greater potency as an anesthetic, it also carries a greater risk of psychotogenic side effects(Yang C. et al., 2015).

Ketamine hydrochloride is a nonbarbiturate dissociative anesthetic. It is a cyclohexanone derivative that is rapidly acting and produces profound anesthesia and analgesia. Its chemical name is ±)-2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride; its structural formula is CHClNO. Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) and glutamate receptor antagonist. It blocks HCN1 receptors. The unique dissociative action and partial agonism on opiate mu-receptors permit the performance of painful procedures in a consistent state of sedation and patient comfort. [18]

Ketamine's effects in chronic pain, and as an antidepressant, far outlast the actual drug levels and are probably mediated by a secondary increase in structural synaptic connectivity that is mediated by a neuronal response to the ketamine-induced hyper-glutamatergic state. [19].

Ketamine may interact with the sigma receptors. It tends to work by decreasing central sensitization, wind-up phenomenon (development of ongoing, worsening, or chronic pain), and pain memory. Cholinergic, aminergic, and opioid systems appear to play both a positive and negative modulatory role in both sedation and analgesia. Ketamine reverses tolerance to opioids. It is metabolized via the hepatic system by way of N-dealkylation, hydroxylation, conjugation, and dehydration. The half-life of ketamine is approximately 45 minutes. [20]

Ketamine generally maintains normal pharyngeal and laryngeal reflexes and, therefore, permits spontaneous respiration. It slightly enhances or maintains normal skeletal muscle tone and is associated with cardiovascular and respiratory stimulation. These characteristics make it particularly useful in the emergency department setting for short-term procedures, especially as is often the case when a patient has not been "prepped" for an emergency procedure. Since there is no guarantee of maintenance of the pharyngeal and laryngeal reflexes, there can be no assumption that they will "protect" the airway. Additionally, there may be transient minimal respiratory depression if the medication is administered too rapidly or in too high a dose. Therefore, the physician must be ready to perform emergency intubation. [18]

Administration and Pharmacokinetics

Ketamine administration can be either IV or IM. The onset of action, when given IV, is within seconds. When administered IM, the onset of action is approximately 4 minutes, with a duration of action from 15 to 30 minutes. [21]

Pharmacology

Ketamine is an arylcycloalkylamine that exists as S(+) and R(−) isomers and is commonly marketed as a racemic mixture of the two (Figure 9). Isolated S(+) ketamine, which is not currently available in the United States but marketed in other parts of the world, has a higher affinity to the binding site on N-methyl-D-aspartate (NMDA)-receptors and produces 3–4 times greater anesthetic potency than the R(−) isomer,When used intraoperatively, the S(+) isomer is associated with less cardiac stimulation, less spontaneous motor activity, better analgesia, more rapid recovery, fewer psychotomimetic side effects, and a decreased incidence of emergence delirium. In the more recent use of ketamine as an antidepressant, mouse studies have shown the R(−) isomer to be more potent and with less side effects than the S(+) isomer [22]

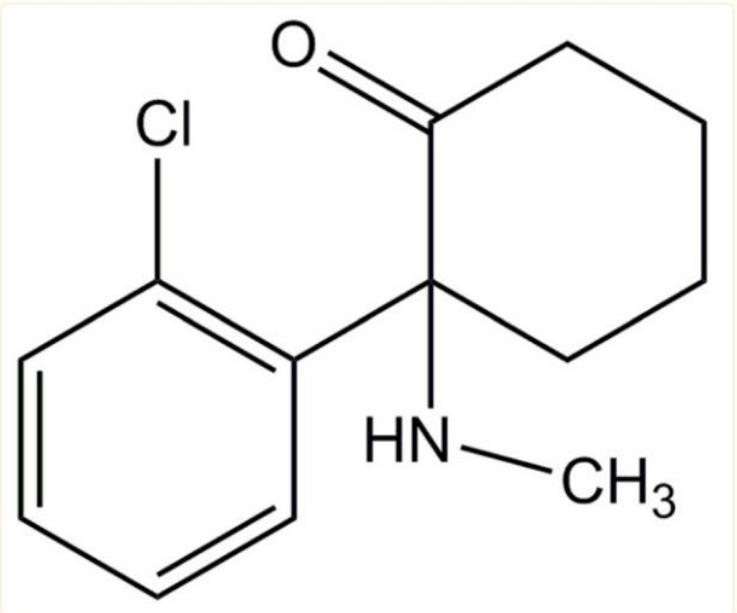


Figure 4: Structure of Ketamine. (Dinis-Oliveira, 2017) [22]

Absorption: Ketamine administered IV exhibits a rapid onset of action, achieving peak plasma concentrations quickly. The IM route of administration provides a high bioavailability of 93% and results in peak plasma levels within 5 to 30 minutes. However, oral ketamine has a significantly lower bioavailability of around 16% to 29% due to extensive first-pass hepatic metabolism. In contrast, intranasal and intrarectal administration of ketamine has demonstrated better bioavailability at 45% to 50% and 25% to 30%, respectively. [23]

Metabolism: Ketamine is primarily metabolized by the enzymes CYP3A4 and, secondarily, the enzymes CYP2B6 and CYP2C9. It undergoes N-dealkylation, hydroxylation, conjugation, and dehydration. [24]

Distribution: Ketamine quickly enters the brain. It has a plasma protein binding from 10% to 50%. The steady-state volume of distribution is 3 to 5 L/kg.

Elimination: Following IV administration, ketamine redistributes from the CNS to peripheral tissues. Its elimination half-life is typically 2 to 4 hours. After administration, most ketamine and metabolites are excreted through urine, with 91% of administered radioactivity appearing over 5 days. Only about 20% occur as the

parent drug or major metabolites. Additionally, hydroxylated metabolites of ketamine and nor-ketamine are eliminated in urine and bile. [22]

Adverse Effects

The most common side effects associated with ketamine are nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, and confusion. There are reports of the emergence phenomenon for approximately 6% to 12% of patients. Rarely patients experience hallucinations.

ADJUVANTS TO LOCAL ANESTHETICS AND BUPIVACAINE

Although beneficial in acute and chronic pain management, local anaesthetics do have the potential to produce deleterious effects like cardiac arrhythmias, central nervous system depression, seizures, respiratory depression, hypertension and allergic reactions.

By prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics, co-administration of adjuvants has the potential to improve efficacy of perineural blocks and decrease local anaesthetic toxicity. The terms, local anaesthetic “adjuvants” or “additives”, have often been used interchangeably. They contribute in their own special manner to potentiate the analgesic effect of the local anaesthetics. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action. [25]

Indications

All local anesthetics contain three structural components: an aromatic ring, a connecting group which is either an ester (procaine) or an amide (bupivacaine), and an ionizable amine group. In addition, all LAs have two chemical properties that determine their activity:

Lipid solubility determines potency, duration of action, and plasma-protein binding of local anesthetics. Local anesthetics enter nerve fibers as a neutral-free base. Ionized forms and the cationic form blocks conduction by their interaction on the inner surface of the Na+ channel. Moreover, LAs with lower pKa has a more rapid onset of action, meaning more of it exists in an uncharged form, which renders faster diffusion to the cytoplasmic side of the Na+ channel.

Conduction of nerve impulses is through the generation of an action potential along an axon, local anesthesia results when LAs bind the Na+ channel and inhibit the Na+ permeability necessary for the action potential. Local anesthetics selectively inhibit the open form of voltage-gated Na+ channels. Na+ channel blockade results in the decrease or elimination of conduction in vascular smooth muscle, leading to relaxation. In the heart, this leads to decreased pacemaker activity and prolongation of the refractory period. This action is unique to bupivacaine due to its decreased rate of dissociation from blocked sodium channels, which leads to prolongation of the maximal rate of depolarization (Vmax) and the potential for ventricular arrhythmias. Also, LAs produce a dose-dependent myocardial depression and interference with Ca2+ signaling within the cardiac muscle because they also bind and inhibit cardiac voltage-gated Ca2+ and K+ channels.

Neuronal tissues have different susceptibility to local anesthetics. Depolarizing currents in nerves move along nodes of Ranvier, and 2 to 3 nodes must be blocked to impair neuronal conduction completely. Smaller fibers have smaller internodal distances and, therefore, get blocked by local anesthetics more quickly. [26]

NALBUPHINE PHARMACOLOGY

Clinical Uses and Mechanism of Action

Nalbuphine

Pruritus is usually secondary to opioid activation of the mu-opioid receptor. Because nalbuphine is an antagonist at the mu-opioid receptor, it has utility as a treatment for opioid-induced pruritus. In fact, research has found that

nalbuphine to be superior in treating opioid-induced pruritus when compared with placebo, diphenhydramine, naloxone, or propofol in patients receiving neuraxial opioids for acute pain related to surgery or childbirth1. [27]

Although nalbuphine can result in respiratory depression, due to its antagonism of the mu-opioid receptor, it antagonizes the respiratory depressant effects of other opioid medications while concomitantly adding to the analgesic activities of these drugs. When used acutely in the perioperative period, nalbuphine is useful for providing analgesic benefits with less respiratory depression than morphine. In one study, researchers used intravenous nalbuphine to reduce opioid-induced respiratory suppression following intrathecal morphine administration in post-thoracotomy patients. [28]

Nalbuphine is a kappa-opioid receptor agonist and a partial mu-opioid receptor antagonist. Analgesic properties are mediated through agonist activity at the kappa-opioid receptor. Because of this unique mixed agonist-antagonist opioid receptor activity of nalbuphine, it provides analgesia with less nausea, pruritus, and respiratory depression when compared to morphine. [29]

Pharmacokinetics and Administration

Absorption: The onset of action of nalbuphine after intravenous injection is 2 to 3 minutes. With subcutaneous or intramuscular administration, the onset of action is within 15 minutes. The duration of action of nalbuphine ranges from 3 to 6 hours.

Distribution: Protein binding not significant.

Metabolism: Nalbuphine is hepatically metabolized.

Elimination: Elimination half-life of about 5 hours. Excreted in urine and feces.

Nalbuphine is available in 10 mg/ml and 20 mg/ml injectable solutions. Nalbuphine is not available in oral form secondary to poor oral bioavailability. [29]

Adjuvant to Local Anesthesia

Nalbuphine is a synthetic highly lipid-soluble opioid analgesic and possesses an agonist action at the κ-opioid receptor and antagonist action at the μ-opioid receptor to provide reasonably potent analgesia of visceral nociception. It is used in almost all types of general and regional anesthetic techniques. Nalbuphine binds to kappa receptors distributed in the spinal cord and brain to produce analgesia. When used as an adjuvant to hyperbaric bupivacaine, it also improves the quality of perioperative analgesia with fewer side effects. It is a mixed synthetic agonist-antagonist, which attenuates the μ-opioid effects and enhances the κ-opioid effects.(Gupta K. et al., 2016)

Nalbuphine, if given systemically, has a reduced incidence of respiratory depression and has been used to antagonize the side effects of spinal opiates. Intrathecal nalbuphine produces lesser adverse effects like pruritus, nausea, and vomiting when compared to intrathecal morphine and does not cause any significant hemodynamic or respiratory complications. [30]

intrathecal nalbuphine potentiated the Subarachnoid block (SAB) characteristics and enhanced the duration of effective analgesia (time from injection to visual analog scale (VAS) score < 3) without affecting the hemodynamic profile of patients. The duration of analgesia was significantly larger by adding nalbuphine as an adjuvant with both the doses, i.e., 1.6 and 2.4 mg, being similar. There were no incidences of pruritus, sedation, respiratory depression, nausea, or vomiting, as these symptoms occur due to the action of the μ receptor. [30]

In research comparing the efficacy of the USG-guided TAP block to the Anatomical landmark technique for postsurgical analgesia after total abdominal hysterectomy, the USG-guided approach produced better outcomes than the Anatomical landmark technique. The study used 0.25% Bupivacaine and 10mg Nalbuphine, with a volume of twenty ml on each side (bilateral). It demonstrated fewer failures, needed less medication, had a quicker onset of pharmacological effect, and had a longer half-life. By attaching to kappa receptors in the central

nervous system, Nalbuphine inhibits the release of pain-related neurotransmitters such as substance P. It also functions as a partial agonist or antagonist at mu receptors and a competitive opioid agonist at kappa receptors. It is an adjuvant to bupivacaine, an amide local anaesthetic that lowers sodium permeability and raises the action potential threshold to impede nerve impulse conduction. Nalbuphine improved the effectiveness of TAP Block and offered better pain management without changing the patients' hemodynamic profile. The interval between an injection and a Visual Analogue Scale (VAS) score of less than four was used to measure adequate analgesia. **(31)**

CONCLUSION

The US-guided technique is considered the gold standard in TAP blocks because it is easy for the operator to acquire US images and safe for the patient to have the procedure performed under direct visualization of the needle prior to the injection of LA. For these techniques, the patient should be positioned supine, except for slight lateralization for the posterior approach in some cases. A high-frequency linear or curvilinear US transducer should be placed in the abdomen with gel for adequate contact and transmission of the US waves. **(9)**

By prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics, co-administration of adjuvants has the potential to improve efficacy of perineural blocks and decrease local anaesthetic toxicity. The terms, local anaesthetic "adjuvants" or "additives", have often been used interchangeably. They contribute in their own special manner to potentiate the analgesic effect of the local anaesthetics. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action. **(25)**

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