INTRODUCTION

The Transversus Abdominis Plane (TAP) Block is a local anesthetic block used to provide analgesia to the anterior and lateral abdominal wall. ***Rafi et al. (2001)*** and ***McDonnell et al. (2004)*** were the first to describe this novel abdominal field block. They described an anatomical landmark technique and provided evidence of blockade to the mid/lower thoracic and upper lumbar spinal nerves as they travelled in the fascial plane between the transversus abdominis and internal oblique muscles. ***Hebbard et al. (2007)*** have subsequently described an ultrasound-guided approach to the TAP block.

Bupivacaine binds to the intracellular portion of voltage-gated sodium channels on the axonal membrane. This prevents inward current of sodium ions without which there is no depolarization of the membrane and consequently no initiation nor propagation of action potentials.

Magnesium, the fourth most common cation in the body, has numerous physiological activities, including activation of many enzymes involved in energy metabolism and protein synthesis ***(James, 1992)***. Magnesium also has antinociceptive effects in animal and human models of chronic pain ***(Feria et al., 1993; Tramer et al., 1996)***. These effects are primarily based on the regulation of calcium influx into the cell, i.e., "natural physiological calcium antagonism" ***(Iseri and French,***

1984) and antagonism of the N-methyl-D-aspartate (NMDA) receptor.

In a clinical study ***Tramer et al. (1996)***, the role of magnesium for postoperative analgesia has been demonstrated. Magnesium administration leads to a significant reduction of naluphine consumption in the postoperative period in patients after lower abdominal surgery. Thus, experimental and clinical data from acute and chronic pain situations demonstrate the effect of magnesium on the pain threshold, which is clinically apparent postoperatively as a reduction of analgesic requirement.

AIM OF THE WORK

The aim of this study is to detect the efficacy and safety of magnesium sulphate as an adjuvant to the analgesia offered by local anesthetic in ultrasound guided TAP block in patients undergoing open appendectomy.

We designed this study to evaluate the effect of adding magnesium sulphate to bupivacaine.25 %in the ultrasound-guided TAP block anesthesia after open appendectomy operation, As regard postoperative pain block and opiod consumption using Visual Analogue Score VAS.

Chapter I

APPENDECTOMY AND PAIN

Appendectomy is one of the commonest abdominal operation performed during emergency hours for acute appendicitis. Acute appendicitis is the common pathology in right lower abdomen. Continuous pain in right iliac fossa even after appendectomy may occur ***(Lamture et al., 2017).***

Assessment of pain

The assessment of pain in the perioperative period is key to the appropriate management of acute postoperative pain. The assessment should start in the preoperative period and should be continued during and after surgery. Different clinical tools, including verbal, visual, and numeric scales and diagrams, have been developed to appropriately assess postoperative pain ***(Sakellariou et al., 2016).***

A) Preoperative pain assessment:-

Preoperative patient-related risk factors have been identified to have an effect on postoperative pain. Hence, clinical interventions targeted at modifying those risk factors may improve postoperative pain ***(Nair et al., 2004).*** Preoperative modifiable and non-modifiable patient factors may influence the development and perception of acute postoperative pain. Example of Non-modifiable preoperative

factors include age, gender, genetic variants, etc. While example of Modifiable preoperative factors include smoking status, alcohol consumption, American Society of Anesthesiologists (ASA) physical status, etc. Preoperative distress and anxiety are important predictors of postsurgical acute and chronic pain ***(Hsu et al., 2005).***

Intraoperative pain assessment:-

Assessing intraoperative pain can be particularly challenging even to the most experienced anesthesia practitioner. There are not objective methods to monitor intraoperative pain in patients under general anesthesia as verbal communication is not feasible in those patients. Anesthesia practitioners have to rely on clinical signs and information obtained from monitoring to assess intraoperative pain. Clinical signs obtained from physical examination include a rise in systemic blood pressure, tachycardia, tearing, extremity withdrawal, and sweating. The clinical scenario is different in patients undergoing surgery under regional anesthesia since they may remain fully awake or mildly sedated and communicative; hence, intraoperative pain monitoring is easier ***(Roth et al., 2015).***

B) Postoperative pain assessment:-

The postoperative quantification of pain is difficult since many psychological factors can influence pain. Pain intensity in

the perioperative period is typically assessed with use of one dimensional scales such as the visual analogue scale (VAS), the four-point verbal rating scale (VRS), or the numeric rating scale (NRS). The three scales can be used to evaluate pain at rest or during motion, coughing, or deep inspiration. Of the three scales the verbal one has the least power to detect a difference in pain intensity. Although the VAS remains the most common tool for assessing pain in the perioperative period, the easiest to use in most patients is the numeric scale, which has numbers from 0 to 10("no pain" to "worst pain imaginable") ***(Levy et al., 2015).***

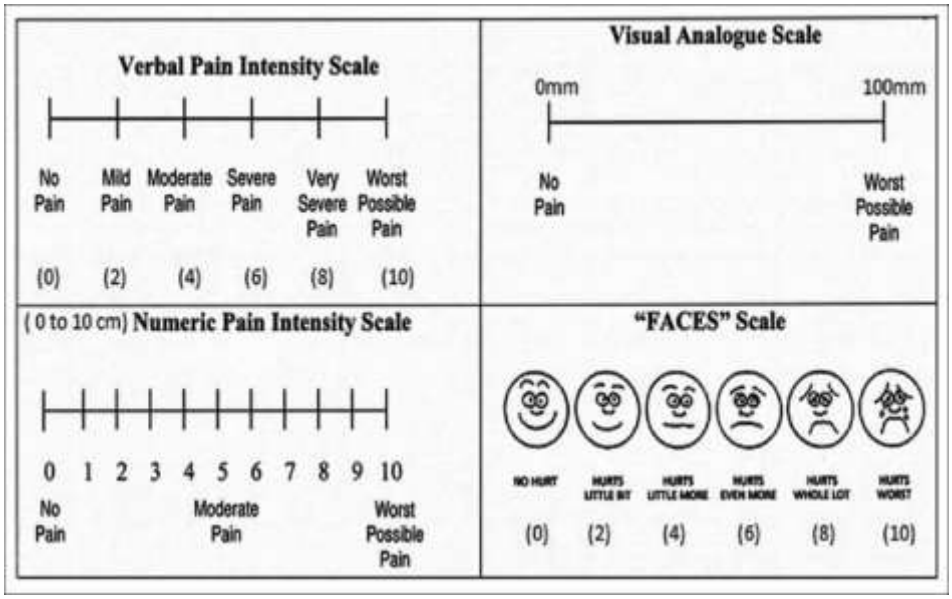

Figure 1: Shows NRS, VRS and VAS as pain assessment scores ***quoted from (Ismail et al., 2016).***

Factors affecting severity of postoperative pain (P.O.P):

Surgical related factors: Site of the surgery has a profound effect upon the degree of P.O.P. Operations in the thorax and upper abdomen are the most painful ***(Razavi et al., 2015).***

Patient related factors: the Nature and intended purpose of surgery If the proposed operation will lead to restoration of a normal function, e.g. hernia repair or fixation of a fracture, it is likely to be seen in positive way by the patient. Other factor as patient personality can affects pain perception and response to analgesic drugs. Thus patients with low anxiety exhibit less postoperative pain and require smaller doses of analgesics ***(Malek et al., 2017).***

Age, gender and body weight can also determine severity of pain. Although, the analgesic requirements of young males and females are identical for similar types of surgery, there is reduction in analgesic requirements with advancing age. In addition, White races need more analgesics than dark races. But, there is no evidence suggesting that variations in body weight in adult population affect opioid requirements. Where the outcome is not clear, e.g. an operation for cancer, patients fear and anxiety may lead to high levels of postoperative pain being reported ***(Malek et al., 2017).***

Management of postoperative pain

Methods used for treating postoperative pain can be classified as:

A- Pharmacological which could be:

1- Systemic

2- Regional

B- Non pharacological

A) Pharmacological methods

1- Systemic:

a) Opioids

Opioids defined as any natural or synthetic drug with morphine-like properties. Opioids are a class of medications that work through agonist of various opioids receptors, including mu, kappa, delta, and sigma. These receptors are located predominantly in the central nervous system, but they exist peripherally as well as seen throughout the body, these receptors are bound by substances that create both a desired effect, analgesia, as well as undesired side effects, including nausea, vomiting and constipation ***(Korenu et al., 2009).***

Table 1: Opioid receptors and their actions

Receptor	Action
Mu1	Analgesia, urinary retention, bradycardia, hypothermia, euphoria
Mu2	Respiratory depression, bradycardia, dependence, euphoria, constipation
Delta	Bound by enkephalins, respiratory depression, dependence, constipation
Kappa	Analgesia, sedation, dysphoria, psychomimetic effects, inhibits ADH release
Sigma	Dysphoria, hypertonia, tachycardia, mydriasis

Quoted from (Korenu et al., 2009)

b- Acetaminophen (Paracetamol)

Acetaminophen is an antipyretic as well as an analgesic that acts centrally by inhibiting prostaglandinS (PG) synthesis. Oral or intravenous acetaminophen combined with opioid had a significant morphine-sparing effect**.**

Acetaminophen is almost entirely metabolized in the liver and excreted in the urine. Paracetamol is contraindicated in patients with severe hepatic impairment, severe active liver disease, or a known allergy to acetaminophen ***(Graham et al., 2005).***

c- Non-steroidal anti-inflammatory drugs (NSAIDs)

These medications act mainly by inhibiting cyclooxygenase (COX) enzyme, which prevents the formation of inflammatory mediators, such as prostaglandins and

thromboxane. Two forms of cyclooxygenase enzymes (COX) have been isolated. COX-1 is present in all tissues, including the gastric mucosa, where it has a protective effect. COX-2 is an inducible enzyme and is produced primarily at the site of inflammation. "NSAIDs' analgesic action appears to be related to inhibition of prostaglandin production both at the site of injury/inflammation and in the central nervous system. Conventional NSAIDs, such as ibuprofen, block both forms of the COX enzymes, while selective COX-2 inhibitors are associated with minimal systemic adverse events ***(Hyllested et al., 2002).***

d- Gabapentin

Gabapentin, as an anticonvulsant, has been found to be useful in many types of neuropathic pain conditions as well as adjuvant for postoperative pain. Gabapentin acts by blocking voltage-dependent calcium ion channels. This mode of action confers its antiepileptic, analgesic, and anxiolytic effects and blunts the development of hyperalgesia and central sensitization ***(Kam et al., 2002).***

e- Ketamine

Ketamine, an N-methyl-D-aspartate NMDA antagonist, has multiple effects throughout the central nervous system, including blocking polysynaptic reflexes in the spinal cord and inhibiting excitatory neurotransmitter effects in selected areas

of the brain. Its ability to block NMDA receptors is thought to improve efficacy of opioids and reduce the development of chronic pain syndromes. While perioperative ketamine decreases opioid consumption ***(Assoluine et al., 2016).***

2- Regional techniques:

Epidural and subarachnoid block: analgesic solution is injected in extradural or subarachnoid space blocking the nerves. These techniques are considered as one of the most beneficial and reliable techniques ***(Cozowicz et al., 2015).***

Peripheral nerve blocks can provide significant pain relief, nerve blocks can be either be combined with general anesthesia or used as the sole anesthetics ***(Honarmand et al., 2015).*** Long acting local anesthetics such as bupivacine or ropivacaine provide nerve block duration of approximately 12-18 hours. Certain additives may prolong this duration for example dexamethasone or methylprednisone may provide additional 6-10 hours ***(Cummings et al., 2011).***

Peripheral nerve blocks seem to lack systemic side effect related to sympathetic blockade and lesser incidence of minor complications including urinary retention when compared with central neuraxial blocks or catheter applications. Peripheral nerve blocks seem to be safer than either central neuraxial blocks or general anesthesia, especially in patients with severe coexisting disease ***(Kettner et al., 2011).***

B) Non-pharmacological techniques:

Many non-pharmacological approaches are thought to decrease postoperative pain:

1- Psychological approach.

2- Physiotherapy.

3- Soft tissue mobilization.

4- Transcutaneous Electrical Nerve Stimulation (TENS).

5- Acupuncture.

Chapter II

PHARMACOLOGY OF LOCAL ANESTHETICS

Local anesthetics are defined as drugs interrupt neural conduction by inhibiting the influx of sodium ions through channels within neuronal membrane ***(Columb and Lennan, 2007).***

<u>Chemistry and structure of local anesthetics:</u>

All commonly used local anesthetics have a three part structure: aromatic (benzene ring), intermediate chain, and amine group. As the intermediate chain contains an ester or an amide linkage, they may conveniently be divided into esters and amides ***(Columb and Lennan, 2007).***

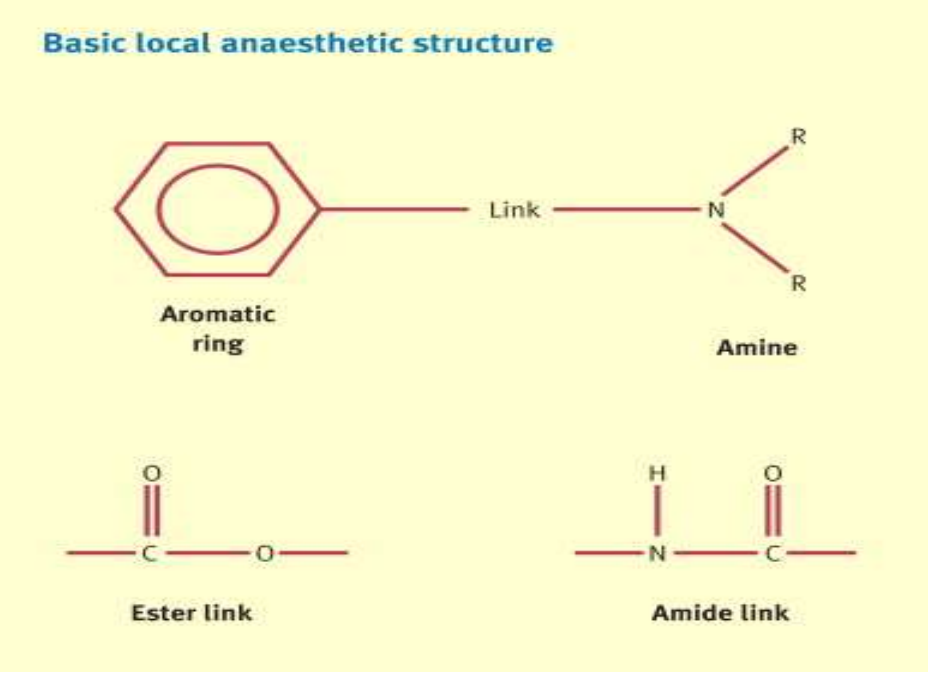

Figure 2: Basic local anesthetic structure *quoted from* ***(Columb and Lennan, 2007).***

Mechanism of action of local anesthetics:

Solutions of local anesthetics are deposited near the nerve. Diffusion of the drug molecules away from the site of injection is a function of tissue binding, removal by the circulation and local hydrolysis of amino ester anesthetics. The result is penetration of the nerve sheath by the remaining drug molecules. Local anesthetic molecules then peretrate the nerves axon membranes. The speed and extent of these processes depend on particular drug's pKa and the lipophilicity of its base ***(Strichartz and Berde, 2005).***

All local anesthetics are membrane stabilizing drugs; they reversibly decrease the rate of depolarization and repolarization of excitable membranes by inhibiting sodium influx through sodium specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels ***(Rosenblatt et al., 2006).***

All nerve fibers are sensitive to local anesthetics, but generally, those with a smaller diameter tend to be more sensitive than larger fibers. Local anesthetics block conduction in the following order: small myelinated axons (*e.g. those carrying nociceptive impulses*), non-myelinated axons then large myelinated axons. Thus, a differential block can be

achieved (*i.e. pain sensation is blocked more readily than other sensory modalities*) ***(Stoelting and Miller, 2000).***

Pharmacodynamics of local anesthetics:

In pure form, weakly basic local anesthetics are largely non ionized and therefore poorly water soluble. Formulation of local anesthetics commercially as hydrochloride salts at a pH of 4.0 to 7.0 greatly increases the ionized fraction, which unfortunately decrease the onset of action, duration and potency of the block. Upon injection into the body, physiological buffer system raises the pH of the solution so that the non-ionized fraction increases. It is the lipophilic natural (non-ionized) free base form of the drug that diffuses across the axon membrane, charged molecules probably gain access to specific receptors on the interior of the neuronal sodium channels via the aqueous pathway of the sodium channel pore, whereas neutral uncharged forms interact with the sodium channels through the lipid environment of the axon membrane ***(Columb and Lennan, 2007).***

Pharmacokinetics of Local Anesthetics:

As local anesthetics are injected in close proximity to the sites of the desired effect, the physical factors (PKa, lipophlicity and ionized & unionized fractions) become much more unimportant than the systemic pharmacokinetic factors ***(Ramamurthi and Krane, 2007).***