COMPARING THE EFFICACY ULTRASOUND GUIDED BILATERAL TRANSVERSUS ABDOMINIS PLANE (TAP) BLOCK BETWEEN 0.25% BUPIVACAINE VERSUS 0.125% BUPIVACAINE IN LAPAROSCOPIC APPENDICECTOMY

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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (ANAESTHESIOLOGY)

UNIVERSITI SAINS MALAYSIA
2017

ACKNOWLEDGEMENT

First of all, I would like to thank the Almighty God who is my great motivator for giving me strength and health to finish this dissertation as partial requirement for my final examination.

Special thanks to my supervisor, Dr Rhenra Hardy Mohamad Zaini, lecturer and anaesthetist at Hospital Universiti Sains Malaysia(HUSM) for his guidance, encouragement and patience over the last two and half years. Thank you so much for forcing me to look at research and my work in difference ways and for opening my mind. Your support was essential for completion my dissertation.

Not to forget, thank you to Dr Wan Mohd Nazaruddin b Wan Hassan as my co supervisor and head of Anaesthesiology Department HUSM for your continuous support.

My deepest thanks and sincere appreciation, to my fellow colleague, especially my buddies who help me in this study, until this work come to existence.

The most importantly, thank you to my beloved family for continuous support and prayer. Your love keep me move forward and stay motivated.

Finally, I humbly extend my thanks to all concerned person who co-operated with me in this journey.

LIST OF ABBREVIATION

ANOVA	ANALYSIS OF VARIANCE
ASA	AMERICAN SOCIETY OF ANESTHESIOLOGY
BMJ	BRITISH MEDICAL JOURNAL
CI	CONFIDENCE INTERVAL
EAES	EUROPEAN ASSOCIATION OF ENDOSCOPIC SURGEON
G PROTEIN	GUANINE NUCLEOTIDES GDP AND GTP
HUSM	HOSPITAL UNIVERSITI SAINS MALAYSIA
IASP	INTERNATIONAL ASSOCIATION FOR STUDY OF PAIN
LA	LOCAL ANAESTHETIC AGENT
NSAID	NON STEROIDAL ANTI INFLAMMATORY DRUG
NYSORA	NEW YORK SCHOOL OF REGIONAL ANESTHESIA
P VALUE	PROBABLITY
PCA	PATIENT CONTROLLED ANALGESIA
PD	PHARMACODYNAMIC
PK	PHARMACOKINETIC
SD	STANDARD DEVIATION
SPSS	STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES
TAP	TRANSVERSUS ABDOMINIS PLANE
VAS	VISUAL ANALOGUE SCORE

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ABSTRAK

Latar belakang

Penyakit appendik akut adalah antara peyebab kesakitan abdomen yang utama yang membawa pesakit ke hospital. Pada hari ini, pembedahan secara laparoskopik menjadi pilihan berbanding secara konvensional. Pembiusan planar "transversus abdominis" terbukti dapat mengawal kesakitan selepas pembedahan bahagian bawah abdomen termasuk pembedahan secara laparoskopic. Walaubagaimanapun, lebih banyak kajian diperlukan untuk mengenalpasti dos optima yang diperlukan dalam mengawal kesakitan selepas pembedahan laparoskopic.

Tujuan

Kajian ini dijalankan untuk mengenalpasti keberkesanan pembiusan planar transversus abdominis kedua dua belah bahagian badan dengan bantuan ultrasound menggunakan ubat bupivacaine 0.125% berbanding bupivacaine 0.25%.

Kaedah

Kajian ini di jalankan secara prospektif ,rawak dan buta dua hala.Secara keseluruhan,44 peserta telah di pilih yang terdiri daripada kumpulan ASA 1 dan ASA 2 untuk menjalani pembedahan appendik secara laparoskopic yang berumur di antara 15 hingga 65 tahun. Peserta telah di bahagi kepada 2 kumpulan secara samarata menggunakan pemilihan berkomputer secara rawak. Sebaik sahaja pembedahan tamat, kumpulan 1 menerima pembiusan planar transversus abdominis dengan bantuan mesin ultrasonografi dikedua-dua bahagian abdomen menggunakan ubat bius setempat 0.25% bupivacaine manakala kumpulan 2 menerima pembiusan yang sama

menggunakan 0.125% bupivacaine. Skala tahap kesakitan menggunakan *visual analogue score* (VAS) dinilai pada 30minit, 4jam, 8jam, 12 jam, 16jam, 20jam dan 24jam selepas pembedahan. Penggunaan *patient control analgesia* (PCA) fentanyl secara keseluruhan di bandingkan antara dua kumpulan. Komplikasi akibat pembedahan secara laparoscopic dan pembiusan planar transversus abdominis di rekodkan.

Keputusan

Perbandingan secara keseluruhan, skala tahap kesakitan (VAS) adalah sama diantara dua kumpulan. Analisis secara ANOVA berulang (*repeated ANOVA*), min perbezaan skala kesakitan (VAS) secara keseluruhan adalah 0.58 {(95% CI -0.17,3.12), nilai p= 0.128, hipotesis null diterima}. Menggunakan analisis statistik independent t-test, perbandingan perbezaan min skala kesakitan(*visual analogue score)* (VAS) 1/2 jam, 4 jam, 8 jam, 12 jam, 16 jam and 20 jam selepas pembedahan menunjukkan keputusan sama diantara dua-dua kumpulan iaitu 0.18(n=44), 0.68(n=44), 0.86(n=44), 0.06(n=40), 0.31(n=28) dan 0.38(n=19) mengikut urutan. Semua nilai p> 0.05, oleh itu, hipotesis null diterima. Tiada perbezaan yang ketara dalam penggunaan PCA fentanyl secara keseluruhan iaitu132.95mcg dalam kumpulan 1 dan 128.64mcg dalam kumpulan 2(perbezaan min 4.32). Penggunaan fentanyl secara keseluruhan untuk kedua-dua kumpulan adalah sangat kecil jika dibandingkan dengan penggunaan fentanyl selepas pembedahan laparoskopik untuk kajian terdahulu. Tiada komplikasi yang berlaku dari pembiusan planar transversus abdominis ini.

Kesimpulan

Pembiusan planar transversus abdominis dengan bantuan ultrasonografi selepas pembedahan laparoskopik appendik menggunakan ubat bius 0.125% bupivacaine adalah sama keberkesanannya berbanding penggunaan ubat bius 0.25% bupivacaine. Penggunaan dos yang rendah berbanding dos biasa bukan sahaja mengurangkan risiko dos toksik, ia juga mengurangkan kos operasi tetapi membekalkan kualiti pembiusan yang setaraf dengan pembiusan menggunakan dos biasa ubat pembiusan setempat. Penggunaan ultrasonografi untuk pembiusan planar transversus abdominis adalah berkesan dan selamat. Ubat penahan sakit oral hendaklah di beri secepat mungkin sebaik sahaja pesakit dibenarkan makan atau minum untuk mengelakkan kesakitan akibat kehabisan kesan bius planar transversus abdominis.

ABSTRACT

Background

Acute appendicitis is a common cause acute surgical abdomenl. Laparoscopic appendicectomy becames more common practise nowadays as compare to open appendicectomy. Transversus abdominis plane (TAP) block is a proven beneficial for post-operative pain control in lower abdominal surgery including laparoscopic surgery. However, more studies are needed to determine effective optimum dose required for post-operative pain control in laparoscopic surgery. This study was aimed to determine the efficacy of 0.125% bupivacaine as compare to standard dose 0.25% bupivacaine in ultrasound guided bilateral transversus abdominis plane (TAP) block for post-operative pain control in laparoscopic appendicectomy.

Method

This study was a prospective, double blinded and randomized controlled trial involving patients came for emergency laparoscopic appendicectomy. Participants were randomized into two groups by using computer assisted randomization. Group 1 received ultrasound guided transversus abdominis plane (TAP) block using 0.25% bupivacaine whereas group 2 received 0.125% bupivacaine immediately after the operation finished. The visual analogue pain score (VAS) were assessed at 30 minutes, 4H, 8H, 16H and 24H post operation. Total PCA fentanyl requirement were compared between these two groups. Complication from the laparoscopic surgery and TAP block was documented.

Result

Overall visual analogue pain score was comparable between these two groups. The overall mean difference in Visual Analogue pain Score(VAS) was 0.58 {(95% CI -0.17,3.12), p value=0.128. Mean difference of VAS at 1/2H, 4H, 8H, 12H, 16H and 20H comparable between these 2 groups which were 0.18(n=44), 0.68(n=44), 0.86(n=44), 0.06(n=40), 0.31(n=28) and 0.38(n=19) respectively. The total PCA fentanyl requirement between both groups were insignificant (132.95mcg vs 128.64mcg) (MD:4.32, p value = 0.73). No complication arises from TAP block.

Conclusion

Ultrasound guided bilateral TAP blocks for post-operative pain control in laparoscopic appendectomy using 0.125% bupivacaine is as effective as 0.25%. Lower concentrations of local anaesthetic reduce risk of toxicity and cost while providing similar post operative analgesia quality. Ultrasound guided TAP block is considered effective and safe with a proper technique. Oral analgesia should be started as soon as possible to prevent breakthrough pain.

1. INTRODUCTION

With the advancement of medical technology, surgical technique continues to develop in parallel to treat diseases. Laparoscopic approach nowadays becomes more popular among surgeon and patients even though in complex surgery. Laparoscopic operation not only offers the advantage of cosmetic effect, it also promotes faster recovery, earlier return to normal activity and reduces hospital length of stay[1, 2].

Pain control started to became a major concern since 1960s and 1970s.However, in the past 35 years, we have seen the development of specialists in this new area of medicine. New concepts and new technologies have led to the development of the field of pain medicine. Since then, pain has been taken as a serious matter and has been studied extensively. Multimodal approaches have been advocated in managing pain as failure to do so will result in more serious problem and may lead to chronic pain[3].

Poorly controlled acute pain after abdominal surgery is associated with a variety of unwanted post-operative consequences, including patient suffering, distress, respiratory complications, delirium, myocardial ischemia, prolonged hospital stay and an increased likelihood of chronic pain [4-6]. Postoperative pain after laparotomy or laparoscopy for colorectal disorders is distressing for patients, and it may result in atelectasis, pneumonia, prolonged postoperative recovery, and delayed discharge (M safey ramen).

Acute appendicitis is among commonest acute surgical abdomen presented to hospital in young population[7, 8]. Pain after surgery for acute appendicitis has two

sources, namely the somatosensory pain originating from the surgical wound on the anterior abdominal wall and the visceroperitonitic pain due to the inflammation of infected appendix[9]. Emergency surgery was needed in most of cases[10]. If the acute appendicitis needs to be treated surgically, there are options to do as open appendicectomy or laparoscopically. Nowadays, with advance development of technology, surgical method had evolved toward less invasive method. Laparoscopic become more common technique in managing surgical appendicectomy. [11].

There is a major concern regarding method of post-operative pain control in abdominal surgery. Transversus abdominis plane (TAP) block is gaining popularity as a method for pain relief after abdominal surgery regardless open or laparoscopic method[12]. The TAP block was first described in 2001 by Dr Rafi, and was further developed and tested by McDonnell et al[13, 14]. The block can be performed blind or using the ultrasound. More recently, ultrasound guided TAP block has been described with promises of better localization and deposition of the local anaesthetic with improved accuracy [15].

Shibata and colleagues assessed the sensory block by pinprick in 26 patients after ultrasound-guided TAP block for laparoscopic gynaecological surgery. They reported a block over the T10–L1 dermatomes and suggested lower abdominal surgery as an indication for TAP block[16]. A meta-analysis on the clinical effectiveness of transversus abdominis plane block in 2009, which was revised in May 2010 concluded that TAP block reduces the need for postoperative opioid use, it increases the time first request for further analgesia, it provides more effective pain relief, and it reduces opioid-associated side effects[17].

Other evidence, a systemic review by Petersen *et al* published in 2010, total of seven randomized, double-blinded clinical trials with a TAP block on post-operative pain were identified. 180 out of 364 patients in these studies received TAP block. The surgical procedures included large bowel resection with a midline abdominal incision, a caesarean delivery via the Pfannenstiel incision, abdominal hysterectomy via a transverse lower abdominal wall incision, open appendicectomy and laparoscopic cholecystectomy with all four ports inserted below the umbilicus. Petersen and his friends concluded that post-operative pain treatment with a TAP block is a promising new technique, demonstrating both a substantial reduction in morphine consumption as well as improved pain scores in surgery involving the anterior abdominal wall[18].

A case study by Mukhtar K, Singh S. has shown that bilateral ultrasound guided TAP blocks in laparoscopic appendicectomy with 20mls 0.25% levobupivacaine deposited between internal oblique and tranversus abdominis muscle on each site provide effective pain relief both intraoperatively and for several hours postoperative period[19]. The use of TAP blocks reduced the need for intraoperative and postoperative opioids and the side-effects associated with their use [12, 14, 20].

However, limited study regarding the efficacy and the dose of local anaesthetic agent required for bilateral ultrasound guided TAP block for post-operative pain control in laparoscopic surgery. Laparoscopic surgery required bilateral TAP block because the abdominal skin incision for the ports of laparoscopic procedure are performed on both sides[21].TAP block is volume dependent. In order to achieve intended level of sensory block, the recommended volume was 20-30mls. In cadaveric study show that the volume of 20mls aniline dye injected by ultrasound guided TAP will reach up to T10 level[22]. In view of requirement of bilateral TAP block in laparoscopic surgery,

minimum total of at least 40mls of local agent needed. There is a major concern regarding the dose of the local anaesthetic agent required.

While bupivacaine is effective as local anaesthetic agent, safety concern emerged when in animal study some deaths related to cardiovascular and or central nervous system toxicity occurred[23]. Therefore the optimum safe dose of local agent required for bilateral ultrasound guided TAP block need to be investigated[17].

This study was conducted to look for effectiveness of a lower concentration of local anaesthetic agent 0.125% as compare to 0.25% bupivacaine in laparoscopic appendicectomy. Previous study done in inguinal hernia patients had use these 2 difference concentration showing equivalent efficacy[24]. By doing this study, ultrasound guided TAP blocks can be incorporated as part of the analgesia regimen for laparoscopic surgery confidently with appropriate safe concentration of local anaesthetic agent. This TAP block was done under ultrasound guided to improve the accurateness of deposited bupivacaine and to improve safety. TAP blocks under ultrasound guidance are easy to perform, provide consistent analgesia, and have displayed a good safety profile.

2 LITERATURE REVIEW

2.1 ACUTE APPENDICITIS

An appendix is a small blind ending tube in between the small and large intestine located at right abdominal quadrant. Acute appendicitis occurs due to inflammation of the appendix for various reasons. It commonly occurs due to obstruction of appendicular lumen by faecolith, normal stool, infective agent or lymphoid hyperplasia. It will cause severe pain and progressive inflammation which can lead to a rupture appendix. Acute appendicitis is among commonest acute surgical abdominal in young patient presented to hospital [7, 8, 25].Generally it is considered as disease of young and it is a second commonest acute abdomen in late adulthood[26]. Overall life time incidence between 7 to 9% (BMJ best practice:acute appendicitis)[27]

Most cases require emergency surgery[10]. In order to avoid rupture of the appendix into the abdomen and causes disseminated infection, patient may need to undergo surgical removal of appendix either open or laparoscopic approach .This operation is called appendicectomy. The traditional surgical approach involves a small incision (about 5 cm or 2 inches) in the right lower abdominal wall known as Mc Burney's technique. Alternatively, it is possible to perform the operation by laparoscopy approach. This is called laparoscopic appendicectomy, requires usually 3 very small incisions (each about 1 cm or 1/2 inch). The surgeon then introduces a camera and instruments into the abdomen and removes the appendix as in the conventional operation.

Even though the laparoscopic technique was introduced more than 100 years ago, it usage initially was limited to diagnostic purpose only [28]. Open appendectomy using

McBurney's technique had become gold standard for surgical treatment of acute appendicitis until 1981, when Semm, a gynaecologist performed appendectomy via laparoscopic approach[29]. Since then, laparoscopic gain attention and has become popular technique. However, despite a lot of advantages, it's practices as the gold standard technique is still controversial. Metaanalysis by Ohtani *et al* conclude laparoscopic surgery may now be the standard treatment for acute appendicitis[11].

Nowadays, laparoscopic technique became the preferred technique due to multiple advantages; it is less invasive, hence less pain and scaring; safer than open surgery, reduces mortality, and reduces hospital stay as it leads to faster recovery [28, 30]. New guidelines by European Association of Endoscopic Surgeons (EAES) encourage laparoscopic approach[31].

The conventional laparoscopic of three ports via the umbilicus, the suprapubic region and the left iliac fossa is currently considered the best approach to achieve proper triangulation[31]. Major contribution to pain during laparoscopic surgery is from tissue trauma at incision sites. The trocar inserted through surgical incision will penetrate muscle and ligaments causing nociceptive pain. If nerve is injured, patient may have neuropathic pain post operation[32]. Three or less small incision made for trocar incision varies depends on surgeon preference. In our centre, 3 trocar inserted; at the umbilicus, suprapubic and left iliac fossa.

2.2 ANATOMY

Abdominal wall innervation originated from spinal nerve. In total, there are 7 spinal nerve supply anterolateral abdominal wall. Six spinal nerve originated from anterior rami of thoracic and one from lumbar[33].These will branches into the intercostal nerves (T7--T11), the subcostal nerve (T12), and the iliohypogastric and ilioinguinal nerves (L1)[33]. The anterior divisions of T7--T11 continue from the intercostal space to enter the abdominal wall between the internal oblique and transversus abdominis muscles. It will continue it course in between internal oblique and transversus abdominis muscle to perforate and supply rectus abdominis muscle.

Subsequently, it will end as anterior cutaneous branches supplying the skin of the anterior abdomen. Midway in its course, it will pierce the external oblique muscle, then giving off the lateral cutaneous branch which it is further divides into anterior and posterior branches. These anterior and posterior branches will supply the external oblique muscle and latissmus dorsi respectively[33]. The anterior branch of T12(subcostal nerve) join with the iliohypogastric nerve to gives a branch to the pyramidalis[33]. The lateral cutaneous branch subsequently perforates the internal and external oblique muscles and descends over the iliac crest and supplies sensation to the front part of the gluteal region[33].

2.3 POST OPERATIVE PAIN

Pain is define by International Association for Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Postoperative pain become a major concern to

patients[34]. Uncontrolled post-operative pain may lead to unwanted clinical and physiological consequences that result in increases morbidity, mortality as well as cost and decrease their quality of life[35].

Pain post-operative appendicectomy originated from 2 sources: somatic pain from surgical wound and visceroperitonic pain due to inflammation and infection[9]. Release mediator (local or systemic) will sensitize C and A delta nociceptor. Fibres from nociceptor will transmit nociceptive information from somatic and visceral to the dorsal horn of the spinal cord. Ascending pathways then relay these information rostrally to thalamic, limbic, and cortical structures[35].

Pain postoperative laparoscopic surgery can be less, similar or more than open surgery [11, 28]. Therefore multimodal approach and preventive analgesia was recommended by Sjovall et al for effective pain control [28]. Multimodal analgesia that can be offered like intravenous analgesia; (ex opioid base, NSAID, Paracetamol), epidural, local anaesthesia at skin incision or nerve block. These different choices of analgesia will block pain pathway at the different site.

2.4 TRANSVERSUS ABDOMINIS PLANE BLOCK

Many study had shown effective result of transversus abdominis plane (TAP) block as part of multimodal approach in abdominal surgery for post-operative pain control[12, 14, 17-20, 33, 36-43].Abdominal wall consists of 3 muscle layer; external oblique, internal oblique and transversus abdominis. TAP block will target spinal nerves that run in between transversus abdominis and internal oblique muscle therefore interrupt sensory innervation to abdominal skin, muscle and parietal peritoneum[33, 44].

However this transversus abdominis plane (TAP) block will not cover the visceral pain as a result of inflammation or surgical incision. Characteristics of visceral pain are as follows; i) it is not evoked from all viscera (organs such as liver, kidney, most solid viscera, and lung parenchyma are not sensitive to pain); ii) it is not always linked to visceral injury (example cutting the intestine, whereas bladder distension is painful stimuli without injury) , iii) it is diffuse and poorly localised; iv) it is referred to other locations; and v) it is accompanied with motor and autonomic reflexes(example such as the nausea, vomiting)[45, 46].Therefore analgesia that are appropriate to be given to cover post-operative visceral pain like opioid based(example morphine, fentanyl) or non-steroidal anti-inflammatory drug(NSAID).

In Laparoscopic surgery, both side of abdomen are involved, therefore bilateral TAP block must be given. TAP block is volume dependent. In order to achieve intended level of sensory blockade, the recommended volume is at least 20mls[22]. Most of study used concentration 0.25% bupivacaine, levobupivacaine or 0.375% ropivacaine[17]. Transversus abdominis plane (TAP) is a vascular area. With high volume deposited at this plane bilaterally, there is a major concern about safety.

Until today, there has been controversy regarding level of spread of injectate following single or multiple injection of transversus abdominis plane block. Mc Donnell *et al* had demonstrated the potential for the TAP block to produce a dermatomes sensory block of T6-L1 afferents in preliminary cadaveric and volunteer studies[44]. Whereas M.J Barrington *et al* had shown involvement of nerve roots T9-T11 following dye injection study in a cadaver model using ultrasound guided subcostal TAP. Spread of injectate also improved with multiple injection technique compared with a single injection technique[47]. Another cadaveric study by Tran *et al*

concludes the involvement of T10-L1following ultrasound-guided TAP injection cephalad to the iliac crest. This implies this technique is limited for lower abdominal surgery[22]. Two techniques of transversus abdominis plane block has been describe; blind landmark technique or ultrasound guided[33].

Blind landmark technique first was describe by Rafi *et al* in 2001[13].In this technique, lumbar triangle of petit will be identified. Anatomically it is describe in between lower costal margin and iliac crest, bounded anteriorly by external oblique muscle and posteriorly by lattisimus dorsi. A point of entry at this petit triangle is made using a blunt needle to appreciate loss of resistance. Double pops will be appreciated as the needle advanced to pass through external and internal oblique[33].

Ultrasound technique has become popular nowadays in most of regional block including TAP block. It allow accurate deposition of local anaesthetic agent at intended area and improve safety[33]. High frequency ultrasound probe (eg.13-6 MHz) is place in between lower costal margin and iliac crest at midaxillary line(Figure1). Using ultrasound, 3 layers of muscle will be identified; external oblique, internal oblique and transversus abdominis muscle (Figure 1). The needle is orientate in plane with ultrasound probe and advanced until it reaches the plane between internal and transversus abdominis muscle. Once the needle tip reach the plane, 2cc of saline is used to confirm the needle position. 20mls of local anaesthetic agent is injected after confirm the placement and it will appear as oval hypoechoeic (Figure 2) in the transversus abdominis plane[33].

Figure 1: Correct placement of ultrasound guided TAP block(*Taken from Journal of NYSORA,Transversus abdominis plane block*)

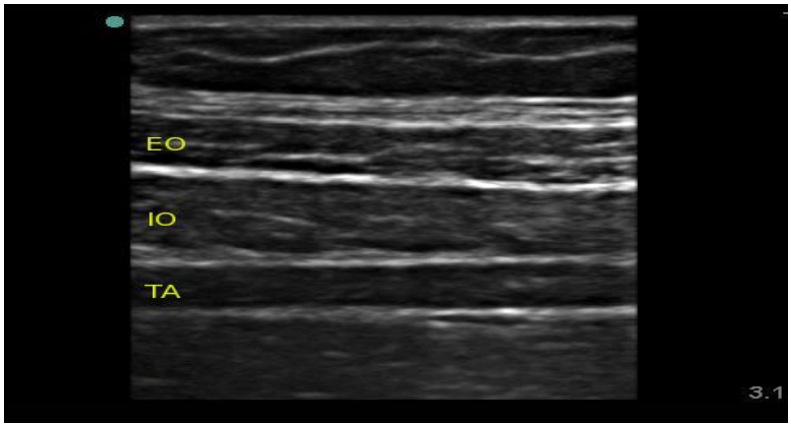

Figure 2: Ultrasound view of anterior abdominal muscle (*Taken from Journal of NYSORA, Transversus abdominis plane Block*)

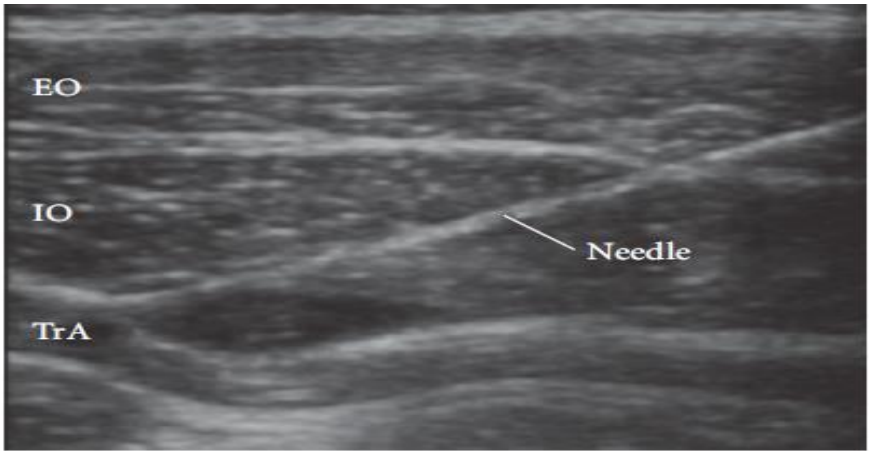

Figure 3: Post injection hypoechoeic at transversus abdominis plane.

2.5 VISUAL ANALOGUE PAIN SCORE

Pain is always subjective and the patient's report is a gold standard. Nowadays there are multiple measures available to assess pain in adult example numerical rating scale and visual analogue pain score. Visual analogue pain score is a continuous scale comprised of a 10 centimetres (100 mm) line in length. It uses a rating scale which usually ranging from 0 (indicating no pain) to 10 (worst pain imaginable). The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity. It has good sensitivity and can provide reliable data for statistical analysis[48]

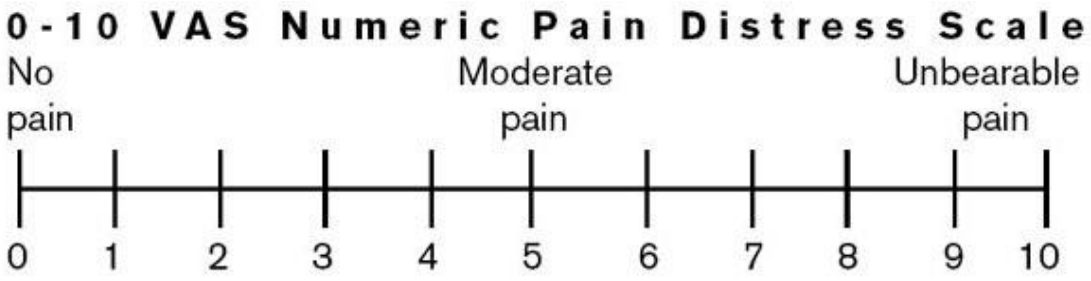

Figure 4: Visual analogue pain score

2.6 LOCAL ANESTHETIC AGENT

Local anaesthetic agents widely being used to block the conduction of pain transmission by reversibly block the Na channel[49].Local anaesthetic agent act by diffuse through the nerve sheath and axonal membrane, get converted into ionized form before it binds to Na+ channel inside the cell. Blocking of Na+ channel prevent nerve membrane depolarization and eventually spread of electrical impulses[50].

Sodium channel appear in 3 state; open activated, open inactivated or closed. The affinity of local anaesthetic for the sodium channel varies with the channel state. The highest affinity is when the sodium channel is open (activated or inactive), and the least when the channel is closed (deactivated and resting). Different local anaesthetic agents have difference affinity towards these sodium channel. For example, lidocaine binds and dissociates rapidly from the channel, whereas bupivacaine binds rapidly, but dissociates more slowly[49]. However, the exact mechanism is more complex as other ion channels such as calcium, potassium and G protein regulated channel also noted being involved[49].

The degree of neuronal block is affected by the diameter of the nerve and its myelination. Small myelinated nerve fibres (pain afferents) require less concentration of local agent than larger diameter fibres (touch/pressure/ motor)[49]. Pain is being transmitted via Aδ and C fibres; while motor function is controlled by Aα and Aβ fibres. Different sensory modalities are lost in the order of pain, temperature, touch, deep pressure then motor function following nerve blockade[49].

Local anaesthetic agent can be administered via subcutaneously or skin infiltration, peripheral nerve block, central blockade (subarachnoid or epidural) or rarely via intravenous biers block.

It can be divided into 2 groups; amide or ester group. Amide is popular group used in clinical practise, as it has less risk hypersensitivity or allergic reaction compare to ester. Example are bupivacaine, lignocaine, ropivacaine or levobupivacaine. Bupivacaine is a synthetic local anaesthetic agent, first introduced in 1963 with chemical configuration similar to first local anaesthetic agent cocaine[50]. It chemical structure is butyl derivative of N-alkyl pipecoloxylidine and structurally related to mepivacaine and ropivacain. It is common local anaesthetic agent used in clinical practise. As compare to other amide members, it is a potent agent with slow onset time but longer duration of action. It becomes popular agent for post-operative pain control for the latter reason.

However, there are concerns about toxicity and difficulty in resuscitation with the high concentration used. The stereo-isomer of bupivacaine(R and S isomer) has different dissociation rates with R-dissociates slowly than S isomer. These differences gives significant risks for cardiac toxicity[49].

Recommended dose varies with procedure, depth of anaesthesia, vascularity of tissues, duration of anaesthesia, and condition of patient (UpToDate). Concentration drug used ranging between 0.25% to 0.75%.

Table 1 : Pharmacodynamics and Pharmacokinetics (Adapted from UpToDate *Bupivacaine 2016*)

Route PKPD	Epidural	Infiltration	Spinal
Onset of action: Anesthesia (route and dose dependent):	Up to 17 minutes to spread to T6 dermatome (Scott 1980)	Fast (Barash 2009); Dental injection: 2 to 10 minutes	Within 1 minute; maximum dermatome level achieved within 15 minutes in most cases
Duration (route and dose dependent):	2 to 7.7 hours (Barash 2009)	2 to 8 hours (Barash 2009);Dental injection: Up to 7 hours	1.5 to 2.5 hours (Hadzic 2007)
Distribution	V_d: Infants: 3.9 ± 2 L/kg; Children: 2.7 ± 0.2 L/kg		
Protein binding	84% to 95%		
Metabolism:	Hepatic; forms metabolite (pipecoloxylidine [PPX])		
Half-life elimination (age dependent):	Neonates: 8.1 hours; Adults: 2.7 hours		
Time to peak, plasma	Caudal, epidural, or peripheral nerve block: 30 to 45 minutes		
Excretion	Urine (~6% unchanged)		
Clearance	Infants: 7.1 ± 3.2 mL/kg/minute; Children: 10 ± 0.7 mL/kg/minute		

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3 OBJECTIVES OF THE STUDY

3.1 GENERAL OBJECTIVES

To evaluate efficacy between 0.25% vs 0.125% bupivacaine in TAP block for post operative pain control in laparoscopic appendicectomy

3.2 SPECIFIC OBJECTIVES

1. To compare mean difference of visual analogue score (VAS) between 0.25% vs 0.125% bupivacaine in bilateral ultrasound guided TAP block for post operative laparoscopic appendicectomy.

2. To compare total requirement fentanyl dose between 0.25% vs 0.125% bupivacaine in bilateral TAP block after laparoscopic appendicectomy.

3. To compare side effect for TAP block between groups who receive 0.25% bupivacaine and 0.125% bupivacaine.

4.0 BODY [MANUSCRIPT READY FOR SUBMISSION] CONTENT:

4.1 TITLE PAGE

4.1.1 ARTICLE TITLE

COMPARING THE EFFICACY ULTRASOUND GUIDED BILATERAL TRANSVERSUS ABDOMINIS PLANE (TAP) BLOCK BETWEEN 0.25% BUPIVACAINE VERSUS 0.125% BUPIVACAINE IN LAPAROSCOPIC APPENDICECTOMY

4.1.2 RUNNING HEAD

BILATERAL TRANSVERSUS ABDOMINIS PLANE (TAP) BLOCK IN LAPAROSCOPIC APPENDICECTOMY

4.1.3 AUTHORS' NAMES AND INSTITUTIONAL AFFILIATIONS

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