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The Efficacy of Pre-Incisional Bupivacaine Infiltration for Post-Operative Pain Relief in Patients Undergoing Appendectomy

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Original Article

Summary

In surgical patients, post-operative pain is the most annoying experience. Previous clinical trials investigated different methods to manage pain postoperatively, however, the effect of pre-incisional administration of bupivacaine infiltration still under debate, hence, we aimed to assess the efficacy of pre-operative bupivacaine infiltration as a part of pre-emptive analgesia in attenuating post-operative pain in patient undergoing open appendectomy. After ethical approval of the study by the Scientific council of Anesthesia and intensive care we conducted this study at Al Sadr medical compound in Najaf, Iraq. The study included 64 patients planned for open appendectomy, and they were randomly assigned into two equal groups. First group (A) infiltrated with 20 cc of 0.5 % plain bupivacaine alongside the line of incision preoperatively after induction of general anesthesia, patients in group B received normal saline instead of bupivacaine as control group. The post-operative pain score at recovery and 2 hours post-operatively were recorded using visual analogue scale (VAS) and compared between groups. Findings revealed a significant lower pain score for the immediate and 2 hours post-operatively in group A than group B, ($p < 0.05$). In conclusion, Pre-operative local infiltration of bupivacaine is an effective and easy way for attenuating post-operative pain in patients undergoing open appendectomy.

Keywords: *Pre-emptive analgesia, Mean Pain score, Appendectomy*

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1. INTRODUCTION

According to the International Association for the Study of pain (IASP), the definition of pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." According to this definition, the interplay between the objective (physiological sensory aspects of pain) and subjective (emotional and psychological) components can be recognized. The response to pain can be highly variable among individuals as well as in the same person at different times (1). Management of post-operative pain has improved in the last four decades. In 2000, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) officially recognized the patients' rights in management of pain including the perioperative pain and put the standards for assessment, monitoring, and treatment of pain (2). In 2004, the American Society of Anesthesiologists (ASA) established the Pain Task Force and published the guidelines to promote standardization of procedures and the use of multimodal analgesia (3). Pain management now has become a focus of the healthcare system and an important ethical responsibility of the medical profession. Opioids remain the primary analgesic agent for treating moderate and severe post-operative pain (4); however, the side effects of opioid are many, and can affect the quality of recovery , and for this reason the application of perioperative multimodal analgesia including the using of peripheral nerve blocks, epidural analgesia and local infiltration of wound had become widely used worldwide. Pre-emptive analgesia is the attenuation of the central sensitization that results from a painful stimuli and the inflammatory reaction that develops after the painful insult by application of an analgesia pre-operatively (4). For effective prevention /attenuation of central sensitization and reduction of post-operative and chronic pain, aggressive multimodal analgesic interventions should be used throughout the perioperative period (5). Maximum benefit occurs when pain reducing interventions are extended into the post-operative phase (6).

Acute Appendicitis is a common surgical emergency that has to be considered in any patient presenting with right iliac fossa pain (7). Approximately 6% of the population undergo appendectomy during their lifetime (8). Appendectomy is the surgical removal of appendix either open method or laparoscopic and it is the only definitive treatment for acute appendicitis (9). Appendectomy is the most common surgical operation performed worldwide therefore much effort has to be directed toward the management of the resulting post-operative pain (10). Widespread recognition of the under-treatment of acute pain by clinicians, health policy experts and economists has led to the development of clinical practice guidelines for expectation ,diagnosis and management of acute pain(11).

Bupivacaine is an amino-amide local anesthetic discovered in 1957 and used clinically for the first time in 1963. The main uses are local infiltration, peripheral nerve blockade, epidural anesthesia/analgesia and Spinal anesthesia (12,13).

***Pain pathways and the neurobiology of nociception*:**

Every surgery produces tissue injury with consequent release of histamine and inflammatory mediators such as bradykinin , prostaglandins , serotonin and nerve growth factor (14). Release of these inflammatory mediators activates peripheral nociceptors, which initiate transmission of nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation, in which release of neurotransmitters (such as substance P and calcitonin gene–related peptide) in the periphery induces vasodilatation and plasma extravasation (14). Noxious stimuli are transduced by peripheral nociceptors and transmitted from peripheral visceral and somatic sites by A-delta and C nerve fibers to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending modulatory input (i.e., serotonin, norepinephrine, γ-aminobutyric acid,enkephalin) occurs (14). Some peripheral impulses pass to the ventral and ventrolateral horns to initiate segmental (spinal) reflex responses, which is associated with increased skeletal muscle tone, inhibition of phrenic nerve function, or even decreased gastrointestinal motility. Other impulses are transmitted to higher centers through the spinoreticular and spinothalamic tracts, where they induce suprasegmental and cortical responses to produce the perception of pain. Sometimes the release of inflammatory mediators in the periphery become continuous and sensitizes functional nociceptors and activates dormant nociceptorsIntense noxious stimuli from the periphery may result in central sensitization ("persistent post injury changes in the CNS that result in pain hypersensitivity" and hyperexcitability ("exaggerated and prolonged responses of neurons to normal afferent input after tissue damage"). Such noxious input can lead to functional changes in the dorsal horn of the spinal cord that may cause post-operative pain to be perceived as more painful than it would otherwise have been (15). The neural pathway in the dorsal horn is extremely complex, and we are just beginning to clarify the specific role of the various neurotransmitters and receptors in the process of nociception. It seems that certain receptors(e.g., N-methyl-d-aspartate [NMDA]) may play important role in the the development of chronic pain after an acute injury, although other neurotransmitters or second messenger effectors such as (substance P, protein kinase C) may also play important roles in spinal cord sensitization and development of chronic pain. Our understanding of the neurobiology of the mechanism of nociception has evolved from the hard-wired system proposed by Descartes in the 17th century to the current view of neuroplasticity in which integration and modulation of nociceptive transmission take place at several levels. However, until now there are many gaps still exist in our knowledge of the specific roles of various receptors,neurotransmitters, and molecular structures in the process of nociception (14). Various noxious stimuli can produce expression of new genes (which are the basis for neuronal sensitization) in the dorsal horn of the spinal cord within 1 hour, and these changes are sufficient to alter behavior within the same time frame (16,17). Also, the intensity of acute post-operative pain is a predictor of chronic post-operative pain (18). Control of perioperative pain by multimodal perioperative management

including the pre-operative preventive analgesia is important in facilitating short and long-term patient convalescence after surgery.

Adverse effects of post-operative pain

Acute Effects

The perioperative period has a variety of pathophysiologic responses that may be initiated or maintained by nociceptive input. At one time these responses may have had a beneficial purposes; however, the same responses to the iatrogenic nature of modern surgery may be so harmful especially in high risk patients (20). Uncontrolled post-operative pain may enhance some of these pathophysiologies and increase patient morbidity and mortality. Attenuation of post-operative pain, by multimodal analgesic regimens, can decrease the perioperative morbidity and mortality. Transmission of nociceptive stimuli from the periphery to the CNS results in the neuroendocrine stress response, a combination of local inflammatory substances (e.g.,cytokines, prostaglandins, leukotrienes, tumor necrosis factor-α) and systemic mediators of the neuroendocrine response (20).

The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical and sympathoadrenal complex interactions. Suprasegmental reflex responses to pain result in increased sympathetic tone, increased catecholamine and catabolic hormone secretion (cortisol, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin, angiotensin II),and decreased secretion of anabolic hormones.20 The resulting effects include sodium and water retention and increased levels of blood glucose, free fatty acids, ketone bodies, and lactate. A hypermetabolic, catabolic state occurs as metabolism and oxygen consumption are increased and metabolic substrates are mobilized from storage depots (20).

The extent of the stress response is influenced by many factors, including the type and intensity of the surgery and the type of anesthesia , with the extent of the neuroendocrine stress response being proportional to the degree of surgical trauma, but the overall response can vary between the patients. The negative nitrogen balance and protein catabolism may hinder the patient convalescence; however, attenuation of the stress response and post-operative pain may facilitate and accelerate the patient's recovery post-operatively (21). The neuroendocrine stress response may enhance detrimental physiologic effects in in all over the body. The stress response is likely a factor in the post-operative development of hypercoagulable state. Enhancement of coagulation (i.e., decreased levels of natural anticoagulants and increased levels of pro-coagulants), inhibition of fibrinolysis, and increased platelet reactivity and plasma viscosity may enhance the incidence of postoperative hypercoagulable-related events such as deep venous thrombosis, myocardial ischemia and vascular graft failure (22). The stress response may also enhance post-operative immunosuppression, the extent of the immunosuppression correlates with the severity of surgical injury (16). Hyperglycemia resulting from the neuroendocrine stress response contribute directly to poor wound healing and supression of immune function and the

resultant prolonged hospital stay. Post-operative pain may activate the sympathetic nervous system and thereby contribute directly to increase the rate of morbidity and mortality. Sympathetic activation increase the myocardial oxygen demand, which is important factor in the development of myocardial ischemia and infarction, and may decrease myocardial oxygen supply through coronary vasoconstriction and attenuation of local coronary vasodilation. Activation of the sympathetic nervous system also delay the return of gastrointestinal motility postoperatively, which may develop into paralytic ileus. Although postoperative ileus is the result of a combination of inhibitory input from central and local factors, an increase in sympathetic efferent activity, such as from uncontrolled pain, may decrease gastrointestinal activity and delay return of the gastrointestinal motility (22,23). Nociceptors are activated after surgical trauma and may initiate several harmful spinal reflexes .Patients with poor post-operative pain control may have shallow breathing ,have an inadequate cough, and be more susceptible to the development of post-operative pulmonary complications and prolonged hospital stay (23).

Chronic Effects

Chronic postsurgical pain (CPSP) is a largely unrecognized issue that may occur in 10% to 65% of post-operative patients (depending on the type of surgery), with 2% to 10% of these patients experiencing severe CPSP (24). Poorly controlled acute postoperative pain is an important predictive factor in the development of CPSP (18, 25) The transition from acute to chronic pain occurs very quickly, and longterm behavioral and neurobiologic changes occur much sooner than was previously thought. Development of CPSP, (18) a causal relationship has not been definitively established, and other factors (e.g., area of postoperative hyperalgesia) may be more important in predicting the development of CPSP (26). One such factor may be the severity of the patient's preoperative pain. Patients with more intense levels of preoperative pain may also develop a degree of CNS sensitization predisposing them to the increased likelihood of higher level of postoperative pain and the subsequent development of chronic pain (26). Thus, it is important that acute pain service clinicians understand chronic pain conditions and involve themselves in the patient's preoperative care. Although the severity of acute postoperative pain may be an important predictor in the increased involvement of the acute pain medicine team in preoperative anesthesia clinics or services can positively attenuate the incidence and severity of post-operative pain. Control of acute postoperative pain may improve long-term recovery or patient-reported outcomes and quality of life. Patients whose pain is controlled in the immediate post-operative period (especially with the use of continuous epidural or peripheral nerve blocks techniques) may be able to actively participate in post-operative rehabilitation, which may improve short- and long-term recovery after surgery (27). Optimizing treatment of acute postoperative pain can improve health-related quality of life (HRQL) (28). Post-operative chronic pain that develops as a result of poor post-operative pain control may interfere with the daily patients' activities.

Pre-emptive Analgesia (preventive analgesia):

The terminology of "preemptive" analgesia referred to any analgesic intervention that preceded a surgical incision and was more effective in relieving acute post-operative pain than the same treatment following the same surgery. The precise definition of preemptive analgesia is one of the major conflicts in this area of medicine and contributes to the question of whether preemptive analgesia is clinically relevant (16). Another Definitions of preemptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury only (i.e., intraoperative period), what prevents central sensitization resulting from incisional and inflammatory injury (i.e., intraoperative and postoperative periods), or the entire perioperative period encompassing preoperative interventions, intraoperative analgesia, and postoperative pain management (i.e., preventive analgesia) (15). The first two definitions are relatively narrow and may contribute to the lack of a detectable effect of preemptive analgesia in clinical trials. The rationale for preemptive analgesia was based on the inhibition of the development of central sensitization. Effectively, noxious input initiated by surgical procedures induced a state of CNS hyperactivity that produce the feeling of pain. Although a very popular and discussed theory, a single analgesic treatment (either peripheral or neuraxial) before the incision does not reduce postoperative pain behaviors beyond the expected duration of the analgesic effect (29) When the block of nociceptive afferents diminishes, the surgical injury is able to reinitiate central sensitization (30). Central sensitization and hyperexcitability can developed after the surgical incision in a patient who has no history of pre-operative pain. Some patients already have existing acute or chronic pain and developed central sensitization before the surgical incision. These patients with preexisting pain usually have even more intense pain in the post-operative period (31). The augmentation of the already preexisting pain can occur especially in acutely hospitalized patients and even in those patients in sub-acute or chronic outpatient settings. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in post-operative pain and rapid

recovery) and long-term (e.g., reduction in chronic pain intensity and improvement in HRQL benefits during a patient's period of convalescence (28). An intervention administered before the surgical incision is not preventative if it is incomplete or insufficient (i.e., central sensitization is not prevented) (30). Incisional and inflammatory injuries are important in initiating and maintaining central sensitization. Limiting the definition of preventive analgesia to the intraoperative (incisional) period only is not relevant or appropriate because the inflammatory response lasts longer into the post-operative period and continues to maintain central sensitization. Maximal clinical benefit is obtained when complete multisegmental blockade of noxious stimuli occurs, with extension of this effect into the post-operative period (31). Preventing central sensitization with intensive multimodal analgesic interventions could theoretically minimize the intensity or even eliminate acute post-operative

pain/hyperalgesia after surgery (18,31). Although there have been a number of clinical trials to study the efficacy of pre-emptive analgesia, it is generally acknowledged that there are only a few randomized controlled double-blind trials in this clinical area of pain research (32).

2. PATIENTS and METHODS

This was a randomized double blind clinical trial conducted at Al Sadr medical compound In Najaf, Iraq from the 10th of September till the end of 15th of December 2019. Sixty four patients aged 18-45 years of American society of anesthesiologists (ASA) physical status of I & II with body mass index (BMI) between 25Kg/m2 and 35 Kg/m2 who met the criteria of acute appendicitis were included in the study, The patients were divided randomly into two groups: **Group A** (preemptive group n=32) received a 20cc of plain bupivacaine 0.5% (maximum dose 3 mg/kg) was infiltrated into the skin and subcutaneous tissue along the proposed line of incision before gridiron incision, then into the external oblique muscle layer before the dissection. **Group B** (control group n=32) patients was infiltrated by 20 cc of normal saline in the same way. A standard anesthetic and post-operative analgesia technique was carried out for all the patients , general anesthesia by propofol 2 mg/kg then atracurium 0.6 mg/kg and maintenance by isoflurane 1.8% paracetamol vial given at the beginning of surgery and ketorolac was given 15 min before extubation as analgesia. Nefopam® was used as a rescue analgesia as requested by the patients in the postoperative ward. All the patient were kept on Diclofenac as a standard post-operative analgesia.

Inclusion criteria:

Patients belonging to American Society of Anesthesiologist (ASA) physical status I & II, aged 18-45 years of either gender with BMI of < 35 kg/m² who required appendectomy under general anesthesia were included.

Exclusion criteria:

Patient was excluded if he/she had one or more of the following:

Chronic diseases like diabetes mellitus, hypertension and asthma or psychiatric illnesses. Obesity grade II (BMI≥ 35 kg/m²), known case of allergy to local anesthetics, surgery lasting more than 1 hour or surgery requiring surgical drain, pregnant and lactating females and noncompliance to the post-operative analgesia standards.

The pain was assessed using the visual analogue score (VAS), which is a 10-cm horizontal line labeled “no pain” at one end and “worst pain imaginable” on the other end. The patients were asked to mark on this line where the intensity of the pain lies. The distance from “no pain” to the patient’s mark numerically quantifies the pain (13). Pain score assessed with VAS twice ; at immediate postoperatively and at two hours after extubation.

Data management and analysis performed using the statistical package for social sciences (SPSS)

version 26. Variables presented as frequencies and percentages for categorical variables and as mean and standard deviation (SD) for scale variables, and appropriate statistical tests applied accordingly at a level of significance of ≤ 0.05.

3. RESULTS

The number of patients in group A (preemptive group) were 32 comprising of 20 (62.5%) male and 12 (37.5%) female. The number of patients in Group B (control group) were 32 comprising of 24(75%) male and 8 (25%) female, (**Figure 1**). The mean age for group A was 24.2 ± 7.61 years, while in group B the mean age was 27.4 ± 10.01 a T test was done and revealed no statistically reliable differences between the mean age of the two groups (P > 0.05) , (**Table 1**). The mean pain for the immediate post-operative period was 2.04 ± 1.15 in group A while in group B it was 4.3 ± 1.02 a t test revealed a statistically reliable difference between the mean pain score of the patients in group A and group B (P <0.05), (**Table 2**). The mean pain for the 2 hours post operatively was 3.11 ± 0.864 for the group A and 4.17 ± 1.23 for group B and a test revealed a statistically reliable difference (P<0.05), (**Table 3**). According to gender wise distribution, male patients were having mean pain of 1.75 ± 1.03 for group A and 4.35 ± 1.04 for group B while Female patient s were having mean pain of 2.54 ±1.21 in group A and 4.25 ± 1.03 in group B for the immediate post-operative period , (**Table 4**). The mean pain for the 2 hours post-operatively male patients were having 3.07 ± 0.74 for group A and 4.375 ± 1.2 for group B while the female the mean pain for the two hours post operatively was 3.192 ± 1.06 in group A and 3.56 ± 0.903 for group B (**Table 5**). A t test was done to correlate between the mean pain score between male and female In group A which was not significant statistically for the immediate pot-operative period and two hours post operatively (P > 0.05).

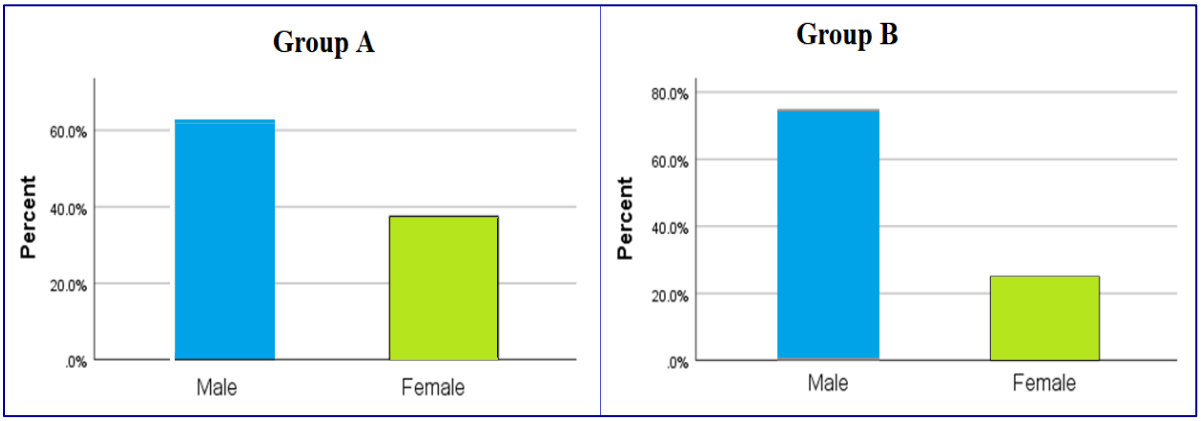

Figure 1. Gender Distribution of the studied groups

Table 1. Age distribution of the studied groups

Variable	Age (year)		P. value
	Mean	SD	
Group A	24.2	7.61	> 0.05 NS
Group B	27.4	10.01	
SD: Standard deviation of mean , NS: not significant			

Table 2. Comparison of mean pain scores of the studied groups at recovery

Variable	Pain score		P. value
	Mean	SD	
Group A	2.04	1.15	P<0.05 Sig
Group B	4.30	1.02	
SD: Standard deviation of mean ,Sig: significant			

Table 3. Comparison of mean pain scores of the studied groups at 2 hours postoperatively

Variable	Pain score		P. value
	Mean	SD	
Group A	3.11	0.864	P<0.05 Sig
Group B	4.17	1.23	
SD: Standard deviation of mean ,Sig: significant			

Table 4. Gender wise distribution of mean pain score of the studied groups at recovery

Variable	Male		Female	
	Mean	SD	Mean	SD
Group A	1.75	1.03	2.54	1.21
Group B	4.3	1.02	4.25	1.03
P. value	> 0.05 NS		> 0.05 NS	
SD: Standard deviation of mean ,NS: not significant				

Table 5. Gender wise distribution of mean pain score of the studied groups at 2 hours postoperatively

Variable	Male		Female	
	Mean	SD	Mean	SD
Group A	3.070	0.74	3.192	1.06
Group B	4.375	1.20	3.56	0.903
P. value	> 0.05 NS		> 0.05 NS	
SD: Standard deviation of mean ,NS: not significant				

4. DISCUSSION

The interest in postoperative pain control has increased in recent decades, when it was noticed that post-operative analgesia was inadequate despite of the advances in understanding pain physiology and the discovery of new analgesic drugs with the development of sophisticated systems for the administration of these drugs. For this reason, a new treatment modalities, such as pre-emptive analgesia, are being incorporated in the management of acute post-operative pain. The pre-emptive analgesia refers to any analgesia modality which is administered before the painful stimulus of surgical incision and prevents or attenuate the subsequent pain resulting from the surgery. Clinical studies have conflicting results regarding the efficacy of pre-emptive analgesia a recent meta-analysis has shown that pre-emptive wound infiltration improved post-operative analgesic consumption and time to first rescue analgesic request. The aim of this study was to demonstrate the efficacy of pre-operative bupivacaine infiltration as a part of pre-emptive analgesia in decreasing post-operative pain. Many studies had examined the efficacy of preoperative bupivacaine infiltration in decreasing post-operative pain in appendectomy, laparoscopic appendectomy, laparoscopic cholecystectomy and these studies showed very good effect. The method of bupivacaine infiltration was easy ,simple and inexpensive mean for providing good analgesia without major side effects as in epidural analgesia. By allowing the patients to mobilize faster therefore the local anesthesia infiltration may be considered as effective as central neuraxia or peripheral nerve blocks in providing post- operative analgesia for certain surgical operations. Untreated or under treated post-operative pain may expose the patient for chronic pain (33). The bupivacaine was used in a way not to exceed the maximum safe dose which is 3 mg/kg.12 All the patients included in the study showed no signs of local anesthetic toxicity and they were monitored for 6 hours after the recovery. The pre-emptive group showed very good result regarding pain scores in the immediate postoperative period and Mean pain score 1.985 ± SD 1.18 compared to 4.445 ± 1.03 for the control group. Meanwhile the pain score

after two hours was 3.085± 0.873 in the preemptive group and 4.21± SD 1.286 we see that the pain score in the 2 groups for the 2 hours postoperative nearly approximate due to the early administration of rescue analgesia in the control group which is the same time at which the fade out of the bupivacaine analgesic effect(duration 120-240 min) (12). The time for first analgesic dose was the standard for the all the patients in the two groups and the rescue analgesia was given as requested by the patient. All of the control group patients requested the rescue analgesia while the pre-emptive group rarely needed rescue analgesia in the 2 hours post-operatively and the time for rescue analgesia was later than the control group . The method of pre-emptive bupivacaine infiltration for appendectomy is a good method for providing immediate post-operative analgesia and it attenuate/prevent the acute and chronic effects of post-operative pain (16,34) Finally the pre-emptive analgesia includes multimodal strategies among them is the pre-operative infiltration of surgical site, so to obtain the optimum benefits a multimodal perioperative analgesia should be considered (3,11).

5. CONCLUSIONS

Pre-operative bupivacaine infiltration is an effective, and easy way for decreasing post-operative pain in patients undergoing open appendectomy for up to 3 hours post-operatively. The method of bupivacaine local infiltration pre-operatively requires no special skills and can provide very good analgesic effects in the immediate post-operative period up to 3 hours post operatively and the duration of analgesia can be maximized using epinephrine .Pain relief can be achieved using multimodal analgesic strategies and the most important is the pre-emptive analgesia including the pre-operative local infiltration of bupivacaine. Perioperative pain relief greatly decrease the risks associated with pain which had been mentioned in this study.For the reasons mentioned above we encourage the use of bupivacaine local infiltration as a part of pre-emptive analgesia in patients undergoing appendectomy under general anesthesia.

Ethical Clearance : The study protocol approved by the Scientific Council of the Iraqi Board of Medical Specialization. Verbal and Signed consents obtained from all patients. Data collection was in accordance with World Medical Association Declaration of Helsinki , 2013, for the ethical principles of researches that involve human. Data kept confidentially and merely used for the purpose of this research.

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