J. Egypt. Soc. Parasitol. (JESP), 45(1), 2015: 177 -182

RANDOMIZED CLINICAL TRIAL COMPARING TWO DIFFERENT TECHNIQUES OF LOCAL ANESTHESIA (SUBCUTANEOUS VERSUS SUBCUTANEOUS & DEEP INFILTRATION) FOR POSTOPERATIVE PAIN IN PATIENTS UNDERGOING OPEN APPENDECECTOMY

By

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Abstract

This study compared the postoperative analgesic effect of local anesthetic (LA) injected subcutaneous (SC) alone versus local anesthetic injected both SC and deep in patients undergoing open appendecectomy operations. Sixty patients ASA class I- II undergoing open appendecectomy for presumed acute appendicitis will be randomly assigned into three groups. After routine monitoring, anesthesia induction was performed with propofol, fentanyl and, cis-atracurium; later, maintenance was continued with isoflurane. GA received local infiltration of the skin prior to incision with bupivacaine 0.25% (10ml), GB received received half the bupivacaine infiltrated into the skin and other half deep-to external oblique prior to incision to create a local nerve field blockade & GC received half dose of saline subcutaneous & half deep to external oblique muscle prior to incision. Postoperative pain was assessed using visual analogue score (VAS) at 1, 4, 8, & 24 hours post extubation. Pethidine 1 mg/kg was given if VAS is ≥4.

All patients in GA (SC) and Control required postoperative analgesics, compared to only 60% of the patients in GB (SC+deep). Time for the first analgesic requirement was prolonged in GB compared to other groups (P<0.01). VAS scores were significantly lower in patients of GB in the first 8 hr. postoperative compared to GA &GC (P<0.01).

Key Words: Appendectomy, pre-incisional infiltration, bupivacaine.

Introduction

Open appendectomy is one of the most frequently performed surgical procedures in the worldwide population and is a cause of significant pain and discomfort in the postoperative period (Jensen *et al,* 2004). Inadequate postoperative pain control may lead to cardiovascular and respiratory complications, prolonged hospitalization and increase health cost (Shang and Gan, 2003). The efficient analgesic regimen should provide safe, effective analgesia, with limited side effects (Jensen *et al,* 2004).

Multimodal approaches to the provision of postoperative analgesia include central neuron blocked (opioids), non-steroid anti-inflammatory drugs, and use of local anesthetics (Fischer and Simanski, 2005). Local anesthetic agent can be applied by using many methods, such as spinal blocks, epidural blocks, periphral nerve blocks and preincisional infiltration (Halaszynski, 2009). The wound infiltration analgesia has become an important part of multimodal analgesia (Andersen *et al,* 2007) to decrease the postoperative pain, improve patient satisfaction, reduce opioid consumption and fasten patient recovery. The use of local anesthetics instead of opioid minimizes opioid side effects postoperative nausea and vomiting (PONV), reduces nursing work, decreases resting pain, enhance early intake of oral fluids and food, and thus reduce patient hospitalization (Vallejo *et al,* 2006).

The surgical incision activate inflammatory, hormonal and immune responses (Giannoudis *et al,* 2006) to administer local anesthetics into wound before the incision (pre-emptive analgesia) was done to reduce postoperative pain by blocking the nociceptive afferent pain pathways of peripheral and central nervous system (Cantore *et al,* 2008). Direct infiltration of the surgical area with local anesthetics was an easier, relatively inexpensive, technically simple and safe for local analgesia (Kerr *et al,* 2008).

Postoperative outcome of the infiltrative treatment is affected by several factors; as the surgery type, infiltration administration time, location, concentration and volume of local anesthetics, adjuvant medications and measurement methods (Otte *et al,* 2008).

The analgesic effect derived from the local anesthetic was due to the constituent drug direct actions as blockage of ion-gated Na channels on A-delta and C-type nerves and therefore nociceptive nerve endings (Hollmann *et al,* 2000).

However, the beneficial effect in terms of pain scores and mobility of the local infiltration analgesia exceeded the expected action duration of the local anesthetic itself; as the local anesthetic drugs might be the reason (Swanton and Shorten, 2003).

The local anesthetics anti-inflammatory effect might be due to several factors including decrease the release of inflammatory mediators from neutrophils reduce formation of oxygen free radicals, decrease neutrophil adhesion to the endothelium and decrease edema formation (Cassuto *et al,* 2006).

Almost all LAs can be effectively used for wound infiltration, but long acting and less toxic LAs are preferred to provide postoperative pain relief (Zinc *et al,* 2008). Lidocaine is one of the amide local anesthetic that has a rapid onset of action and an intermediate duration of efficacy. It also can be used as anti-arrhythmic, analgesic and anti-inflammatory drug. Its most side effects as an anesthetic drug are related to administration technique and result in central nervous system excitation and cardiovascular toxicity (Yardeni *et al,* 2009). Bupivacaine with its long lasting effect is most commonly injected into surgical wound sites for the relief of postoperative pain (Lohsiriwat *et al,* 2004; Edwards *et al,* 2011). Exposure to excessive quantities result into systemic toxicity in the form of central nervous system excitation and cardiovascular effects, including hypotension, bradycardia, arrhythmias, and/or cardiac arrest (Roberge *et al,* 1998). Levobupivacaine is an S-isomer of racemic bupivacaine that has emerged as a safer alternative for regional anesthesia. It has recently been introduced as a promising long-acting local anesthetic with a lower toxicity than bupivacaine (Crina *et al,* 2008). Ropivacaine was likely chosen for its reduced cardiotoxicity in comparison to bupivacaine as well as for its intrinsic vasoconstrictor properties (Gutton *et al,* 2013). Thus, bupivacaine has been superceded by levobupivacaine or ropivacaine, both of which have less ability to produce cardiovascular depression and seizure activity because of overdose or intravascular injection, especially in neonates, children, or pregnant women (Ozmen *et al,* 2011; Gutton *et al,* 2013).

In this study, 0.25% bupivacaine was used as the local anesthetic for wound infiltration to provide post-operative pain relief. It is most commonly injected into surgical wound sites with longer half-life than lidocaine, and can potentially provide relief of postoperative pain for up to 20 hours after the surgery.

Material and Method:

This study was conducted after approval of the institutional ethical committee and obtaining an informed written consent from every patient. The study involved sixty adult patients aged 25-65 years of either sexes ASA class I & Π undergoing open appendectomy for acute appendicitis. They were randomly assigned into three groups. GA received local infiltration of the skin prior to incision with bupivacaine 0.25% (10ml). GB received half the bupivacaine infiltrated into the skin and the other half deep-to the external oblique prior to skin incision to create a local nerve field blockade. GC (control group) received 10 ml of saline, 5ml infiltrated into the skin and other 5ml deep-to external oblique prior to skin incision.

All patients were monitored using routine monitoring including: 5 lead ECG, non-invasive blood pressure monitoring, pulse oximtrey, capnography, and anesthetic gas analyzer. All patients received standard general anesthesia with propofol 2 mg/kg, cis-atracurium 0.15 mg/kg & fentanyl 2ug/kg. Anesthesia was maintained with isoflurane 1 % + 30% oxygen in air & controlled mechanical ventilation to maintain ends tidal CO2 between 35-40 mmHg. Muscle relaxation was maintained by cis-atracurium by the rate 0.02 mg/kg.

In post anesthesia care unit (PACU), postoperative pain was assessed using visual analogue score (VAS) on a 0 to 10 scale where a score of 0 represents no pain and 10 is the worst pain imaginable. VAS was measured at 1, 4, 8, &24h post extubation. Whenever the VAS score ≥ 4 or the patient requested pain medication, analgesia was provided by pethidine 1mg/kg intramuscular. Number of patients required analgesia and the time to first analgesic requirement were recorded.

Statistical analysis: Data were expressed as M±S deviation (SD). Comparison between the mean values of the two groups was done using Mann-Whitney U test while comparison relative to the baseline in the same group were performed using Friedman's ANOVA with post hoc Wilcoxon matched pairs test. P= less than 0.05 was significant.

Results

Among the 60 patients, there were no significant differences between groups in demographic variable (Tab. 1). All in GA and GC required postoperative analgesics, while in GB (SC+ deep), only 40% didn't require analgesia postoperatively. Time for the first analgesic requirement was prolonged in GB compared to GA & GC (Tab. 2). VAS scores were significantly lower in GB in the first eight hr. postoperative compared to GA & GC, without great difference in value at eight hr. postoperative between all groups. The VAS was lowered again in GB at 24 hr. postoperative compared to GA & GC (Fig. 1).

Table 1: Demographic features of studied group.

	GA (n= 20)	GB (n= 20)	GC (n= 20)
Age (yrs.)	22.8 ± 4.5	23.8 ± 6.36	23.75 ± 4.29
Sex (F/M)	17/3 (85%/15%)	18/2 (90%/10%)	17/3 (85%/15%)
BMI	27.5 ± 2.19	27.65 ± 2.70	27.25 ± 2.79
ASA class (1)	17/3 (85%/15%)	18/2 (90%/10%)	17/3 (85%/15%)

GA = subcutaneous group GB = subcutaneous+ deep group GC = control group

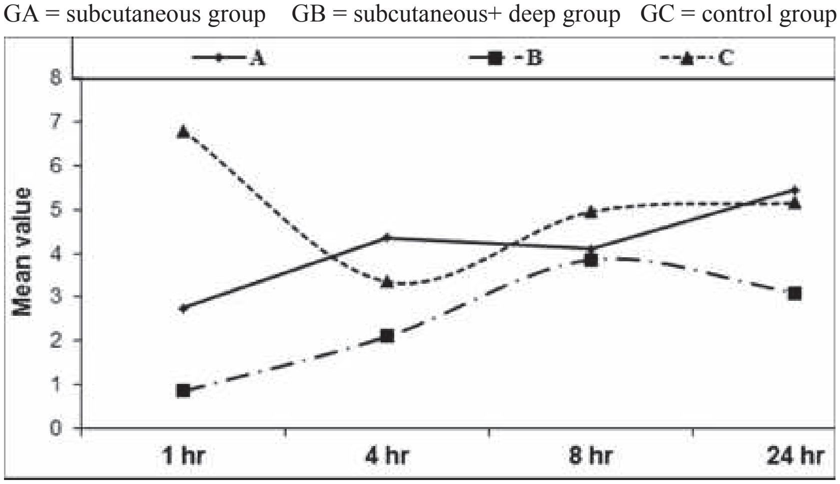

Fig 1: Mean VAS measured after different duration time of surgery among groups.
[a]p< 0.01 relative GC, [b]p< 0.01 relative SC GA

Table 2: Postoperative Pethidine requirements in groups.

	GA (n= 20)	GB (n= 20)	GC (n= 20)
Patients didn't require postoperative analgesia	0 (0%)	8 (40%)	0 (0%)
1 hr	4 (20%)	0 (0%)	18 (90%)
4 hr	11 (55%)	1 (5%)	1 (5%)
8 hr	5 (25%)	10 (50%)	1 (5%)
24 hr	0 (0%)	1 (5%)	0 (0%)

P< 0.01

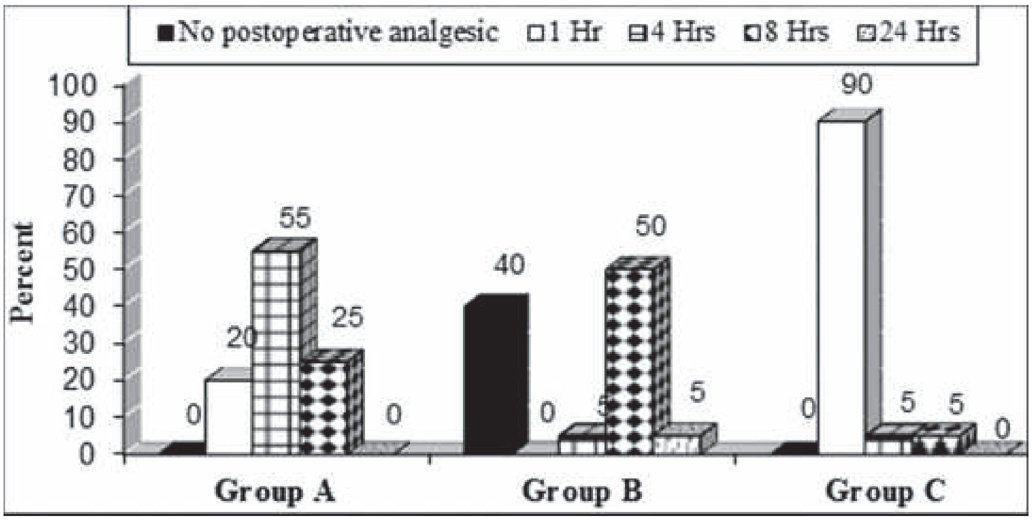

Fig 2: Statistical comparison of groups comparing postoperative pethidine requirement at 1, 4, 8 & 24 hr. and patients who didn't require analgesia

Discussion

This study revealed that injection of local anesthetic both SC and deep infiltration in patients undergoing open appendicectomy opertations reduced postoperative pain score, analgesic requirements and the number of patients required analgesia together with prolonged postoperative analgesic duration compared to SC injection of local anesthetic and control group.

The results agreed with many trials about the efficacy of pre-emptive anesthetic infiltration. Cherian *et al.* (1997) used 0.375% bupivacaine infiltrated to the muscle and subcutaneous tissue before closure of the incision line in unilateral laminectomy patients due to lumbar disc hernia. Postoperative elapsed time for the requirement of the first analgesics was 807.7 & 181.4 minutes in the bupivacaine-infiltrated and controls respectively and concluded that this method was effective and safe. Bagul *et al.* (2005) infiltrated the subcutaneous tissues with 10ml of 0.5% bupivacaine pre-incisional in thyroidectomy patients, and found that pain scores were lower in bupivacaine-infiltrated compared to controls, at the first six hr., but without any difference at the 24th hr. Morphine was not needed in the bupivacaine group, but it was 25% in the controls. They concluded that bupivacaine-infiltration was easy and gave good pain control on thyroidectomy patients, without any unfavorable effect on wound healing. Also, Cervini *et al*. (2002) used 0.5% bupivacaine and reported the benefit of preemptive bupivacaine infiltration that resulted in a decreased need for postoperative parenteral narcotics.

On the contrary, Ko *et al*. (1997) used a combination of lidocaine hydrochloride and bupivacaine hydrochloride and found no benefits in reducing postoperative pain and analgesic requirements or in shortening hospital stay length. This might be due to the differences in technique of anesthetics infiltration as not included the abdominal muscular layer, but only the subcutaneous tissue.

Similar results in terms of consumption of opioids were reported (Cobby *et al*, 1997; Johansson *et al*, 2000; Klein *et al*, 2000; Updike *et al*, 2003) as VAS scores and time for additional analgesics between groups administered local anesthetics to the superficial or deep layers of abdomen and controls. However, with local anesthetics injected to all abdominal layers, the requirement of postoperative opioids decreased.

In pediatric appendectomy Edwards *et al*. (2011) reported that 0.25% bupivacaine administration gave no additional benefit over regular simple analgesia, but this might be due to the fact the wound infiltration technique did not include the abdominal muscle layer, but used neurovascular plane and subcutaneous tissue prior to skin closure. Others (Cherian *et al,* 1997; Cervini *et al,* 2002; Bagul *et al,* 2005) used 0.5% bupivacaine and recommended the higher concentrations (0.375% to 0.5%) than the smaller one 0.25 % used in this study.

Conclusion

The injection 0.25% bupivacaine both SC and deep infiltration in patients undergoing open appendicectomy opertations provided less postoperative pain score, analgesic requirements and number of patients required analgesia and prolonged analgesic duration together with better patient's satisfaction score when compared to only SC injection of local anesthetic group and the control group.

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