Pre-incisional peritonsillar infiltration of tramadol and bupivacaine improves outcome of tonsillectomy in adult patients

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Abstract: Objectives: To evaluate postoperative (PO) analgesic efficacy of pre-incisional peritonsillar infiltration (PI) using tramadol alone or in combination with bupivacaine in adults assigned for tonsillectomy. **Patients & Methods:** Eighty patients were allocated into four equal groups: Control group received saline, Bupivacaine group received bupivacaine (5 mg/ml), Tramadol group received tramadol (2 mg/kg b.wt.) and Combination group received combination of bupivacaine and tramadol. All medications were injected as 1 ml per tonsil 3 min prior to incision (pre-incisional). Evaluated parameters included duration of PO analgesia and PACU stay and total hospital stay. Postoperative pain sensation was evaluated using 10-points visual analogue scale (VAS) score and rescue analgesia (morphine 0.05 mg/kg i.v.) was administered at VAS score ≥4. Patients were asked to rate their satisfaction with analgesia on a 7-point scale. **Results:** All patients had smooth intraoperative within mean operative time of 62±4.9 minutes and mean intraoperative blood loss of 41.7±4.7 ml. Collective VAS pain scores were significantly higher in control group compared to other groups, while combination therapy provided significantly lower pain scores compared to tramadol alone or bupivacaine alone. Twenty-five patients were discharged without requesting rescue analgesia. Combination therapy provided better PO analgesia lasting for longer duration with significant difference compared to other groups. Duration of hospital stay was significantly shorter in patients received infiltration therapy compared to control group with significantly shorter duration with combination therapy. Patients received infiltration therapy were significantly satisfied compared to control group with significantly higher satisfaction scores in combination and tramadol groups compared to bupivacaine alone. **Conclusion:** Pre-incisional peritonsillar infiltration is a safe and effective analgesic modality for post-tonsillectomy pain in adults and combined bupivacaine and tramadol infiltration is the appropriate for achieving superior postoperative analgesia.
[Mohamed F. Shindy and Tamer S. **Abd El-Hamid. Pre-incisional peritonsillar infiltration of tramadol and bupivacaine improves outcome of tonsillectomy in adult patients**. *J Am Sci* 2014;10(8s):46-54]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 5

Keywords: Tramadol, Tonsillectomy, Adults, peritonsillar infiltration

1. Introduction

Tonsillectomy is the commonest operative procedure among otolaryngologists, limited data exist with respect to the current prevalence of indications for tonsillectomy in adults; however, chronic infection remains the most common indication for adult tonsillectomy with complication rates varied according to the indication for surgery **(Eisenach, 2006; Ozkiriş *et al.,* 2013)**.

Postoperative (PO) pain has not only a pathophysiologic impact but also affects the quality of patients' lives. Post-tonsillectomy pain especially in adults still constitute one of the famous annoying complaints for both patient and surgeon and were the principal cause of morbidity after tonsillectomy **(Hoddeson & Gourin, 2009; Inci *et al.,* 2009)**. In addition, PO pain was found to be a leading cause for multiple surgical morbidities **(Park *et al.,* 2007)**. **Sarny *et al.* (2012)** reported that patients who have severe or increasing pain in the first few days after tonsillectomy have a significantly higher risk of hemorrhage and adequate analgesia, for the first week post-tonsillectomy, is essential in order to keep the secondary hemorrhage rate within an acceptable range.

Improved pain management might therefore speed up recovery and rehabilitation and consequently decrease the time of hospitalization. Surgery causes tissue damage and subsequent release of biochemical agents such as prostaglandins and histamine. These agents can then stimulate noci-receptors, which will send the pain message to the central nervous system to generate the sensation of pain. Neuroendocrine responses to pain can also cause hypercoagulation state and immune suppression, leading to hypoglycemia, which can delay wound healing **(Guptarak *et al.,* 2013; Dubový *et al.,* 2013; Schmidt *et al.,* 2013)**.

The exact cause of post-tonsillectomy pain is a matter of controversy, area innervation disorders including variability of pain threshold, large exposed raw tonsillar bed, damage of bed muscle fibers due to preoperative fibrosis and postoperative clumsy dissection were reported as possible causes of severity of post-tonsillectomy pain (**Stelter *et al.,*** 2009).

Review of literature reveled a great discrepancy regarding the efficacy of peritonsillar infiltration of

local anesthetics as a modality for post-tonsillectomy analgesia; **Costas-Gastiaburo *et al.* *(1998)*** found peritonsillar infiltrations decrease intra-operative bleeding and pain, independent of the type of solution infiltrated; while **Nordahl *et al.* (1999)** and **Vasan *et al.* *(2002)*** found no statistical significant benefit for use of preincisional bupivacaine in tonsillectomy as regards postoperative pain at any time interval in comparison to saline injection. However, combining local anesthetic agents with other drugs such as adrenaline, clonidine, ketamine or various opioids have met with varied degrees of success **(Tripi *et al.*, 2005)**.

Thus, the current prospective comparative study aimed to evaluate the PO analgesic efficacy of pre-incisional peritonsillar infiltration using tramadol alone or in combination with bupivacaine in adults assigned for tonsillectomy.

2. Patients & Methods

The present study was conducted at Departments of Otorhinolaryngology and Anesthesia, FMC, Abu Dhabi, Emirate since June 2010 till Aug 2012. After approval of the study protocol by the Local Ethical Committee and obtaining fully informed written patients' consents, all adult patients assigned for tonsillectomy for chronic tonsillitis were included in the study.

Patients with cardiovascular disease, hypertension, bleeding diathesis and those administering aspirin or other medications affecting coagulation system and patients with kidney or liver dysfunctions, as well as anemia (Hb<10g/dl) were excluded from the study. Patients had allergy to study drugs or tonsillar abscesses were also excluded from the study.

Eighty patients were randomly, using sealed envelops, allocated into four equal groups (n=20): Control group included patients assigned to receive PT saline infiltration as placebo, Bupivacaine group included patients assigned to receive bupivacaine (5 mg/ml) PT infiltration, Tramadol group included patients assigned to receive tramadol (2 mg/kg) PT infiltration and Combination group included patients assigned to receive PT infiltration using a combination of bupivacaine (5 mg/ml) and tramadol (2 mg/kg). All medications were prepared as 2 ml in volume and were injected as 1 ml per tonsil 3 min prior to incision (pre-incisional).

All study patients were premedicated with 0.05 mg/kg midazolam intravenously before the procedure and received fentanyl 1 μg/kg i.v. immediately after induction of general anesthesia using IV propofol 2–3 mg/kg. Anesthesia was maintained, in all groups with sevoflurane in an oxygen/nitrous oxide mixture at a total fresh gas flow of 1 liter/min, titrated to keep mean arterial pressure within 20% of baseline values. No additional opioids or non-steroidal analgesics were administered intra-operatively. Intra-operatively, antibiotic prophylaxis using broad spectrum antibiotic was conducted and dexamethasone was received in a dose of 1 mg/kg up to a maximum of 20 mg/kg.

All patients were cared postoperatively at PACU and the efficacy of PO analgesia after PT infiltration was judged using the following items: duration of PO analgesia defined as the time since end of surgery till the first request of rescue analgesia, duration till be ready to discharge from PACU defined as time since end of surgery till achieving an Aldrete score of 9 using 5-items, scored from 0 to 2, namely: respiration, blood pressure, activity, consciousness and O_2 saturation, (Table 1) (**Aldrete, 1995**) and duration till return home.

Postoperative pain sensation was evaluated using 10-points visual analogue scale (VAS) score which was evaluated at time of admission to PACU and every 15 min for one hour and every 30 minutes till patients were ready for discharge from PACU. Rescue analgesia with morphine 0.05 mg/kg i.v. was administered, after operation; for VAS score ≥4 or if the patient requested analgesia during pain assessment. At time of home-return, patients were asked to rate their satisfaction with analgesia on a 7-point scale; 1 being extremely dissatisfied and 7 being extremely satisfied **(Alhashemi & Kaki, 2004)**.

Table (1): Constituents Parameters of Aldrete score (Aldrete, 1995)

Score Item	0	1	2
Respiration	Able to breath deeply & cough freely	Dyspnea or limited breathing	Apnea
Blood pressure	±20% pre-operative value	±20-49% pre-operative value	±50% pre-operative value
Activity	Able to move 4 limbs voluntarily or on command	Able to move 2 limbs voluntarily or on command	unable to voluntarily move limbs or on command
Consciousness	Fully awake	Arousable on calling	Not responding
O_2 saturation	>92% on air	>90% with O_2 supplement	<90% even with O_2 supplement

3. Results

The study included 80 patients; 51 males and 29 females with mean age of 31.5±8.4; range: 21-48 years. All patients had smooth intraoperative course without complications. Mean intraoperative blood loss was 41.7±4.7; 26-50 ml. Mean operative time was 62±4.9; range: 45-70 minutes. There was a non-significant (p>0.05) difference between studied groups as regards patients' demographic data (Table 2) or intraoperative blood loss and operative time, (Table 3).

Collective VAS pain scores determined since admission to PACU till hospital discharge were significantly (p<0.001) higher in control group compared to the other studied groups. On contrary, combination therapy provided significantly lower VAS pain scores compared to tramadol alone (p=0.002) or bupivacaine alone (p=0.001), with non-significantly (p >0.05) higher VAS scores with bupivacaine alone compared to tramadol alone, (Table 4).

Twenty-five patients (31.3%) were discharged without requesting rescue analgesia; 40 patients (50%) requested rescue analgesia once; 12 patients (15%) requested it twice and only 3 patients (2.5%) in control group requested rescue analgesia for 3 times, (Fig. 1).

Combination therapy provided better PO analgesia manifested as no request of rescue analgesia in 65% of patients, while 35% of patients requested it once with significantly (p <0.001) higher frequency of patients did not request rescue analgesia compared to other modalities of analgesia. Both tramadol and bupivacaine provided significantly (p <0.001) higher frequency of patients did not requesting rescue analgesia or requesting it once compared to control group with non-significant (p >0.05) difference between tramadol and bupivacaine. No patients received infiltration analgesia requested rescue analgesia trice, while 3 patients in control group required it for three times, (Table 5).

Among patients requested rescue analgesia (n=55) patients received combined therapy requested it after significantly (p <0.05) longer duration compared to other studied groups. Patients received either tramadol or bupivacaine alone showed significantly (p <0.05) longer duration of PO analgesia compared to placebo with non-significantly (p >0.05) longer duration of PO analgesia between tramadol and bupivacaine groups, (Fig. 2).

Table (2): Patients' demographic data

	Age (years)	Sex (M:F)	Body weight (Kg)
Control group	32±7.2 (23-42)	9:6	82.3±4.9 (72-89)
Bupivacaine group	31±8.7 (21-44)	11:4	83.9±4.5 (76-90)
Tramadol group	32±9.3 (21-45)	10:5	85.6±5.4 (75-92)
Combination group	30.6±8.7 (22-48)	8:7	85.2±3.8 (80-91)
Total	31.5±8.4 (21-48)	51:29	84.3±4.8 (72-92)

Data are presented as mean±SD & ratios; ranges are in parenthesis

Table (3): Intraoperative blood loss and operative data

	Intraoperative bleeding (ml)	Operative time (min)
Control group	39.8±6.9 (30-45)	61.9±5.1 (45-65)
Bupivacaine group	41.4±5.9 (26-50)	61±5.2 (50-65)
Tramadol group	42.1±3.9 (29-45)	61.5±3.6 (55-65)
Combination group	43.5±3.4 (35-50)	63.6±5.5 (50-70)
Total	41.7±4.7 (26-50)	62±4.9 (45-70)

Data are presented as mean±SD; ranges are in parenthesis

Table (4): Mean collective VAS scores determined in studied groups

	Control group	Bupivacaine group	Tramadol group	Combination group
Mean±SD	2.5±0.37	1.7±0.45	1.6±0.32	1±0.56
Z		3.787	3.939	3.927
P_1		<0.001	<0.001	<0.001
Z			1.777	3.301
P_2			>0.05	=0.001
Z				3.081
P_3				=0.002

Data are presented as mean±SD; p_1: significance versus Control group; p_2: significance versus Bupivacaine group; p_3: significance versus Tramadol group

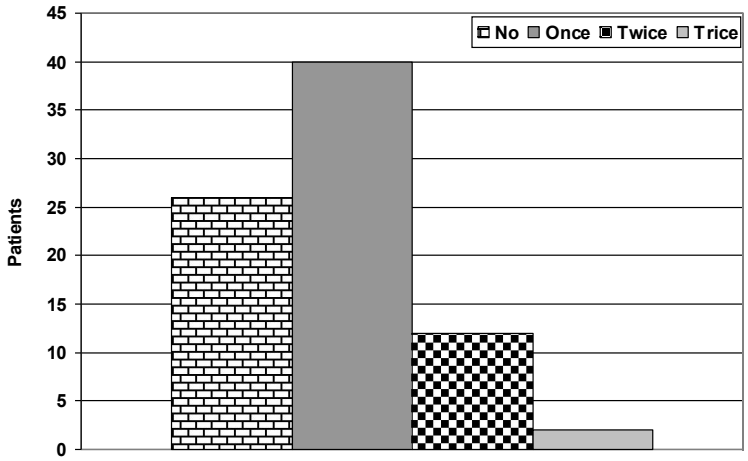

Fig. (1): Patients' distribution according to frequency of requesting rescue analgesia

Table (5): Patients' distribution according to the frequency of requesting rescue analgesia in studied groups

		Control group	Bupivacaine group	Tramadol group	Combination group
No		0	7 (35%)	5 (25%)	13 (65%)
Once		10 (50%)	11 (55%)	12 (60%)	7 (35%)
Twice		7 (35%)	2 (10%)	3 (15%)	0
Trice		3 (15%)	0	0	0
Statistical analysis	X^2		45.66	22.285	166.178
	P_1		<0.001	<0.001	<0.001
	X^2			1.478	10.463
	P_2			>0.05	<0.001
	X^2				20.383
	P_3				<0.001

Data are presented as mean±SD; p_1: significance versus Control group; p_2: significance versus Bupivacaine group; P_3: significance versus Tramadol group

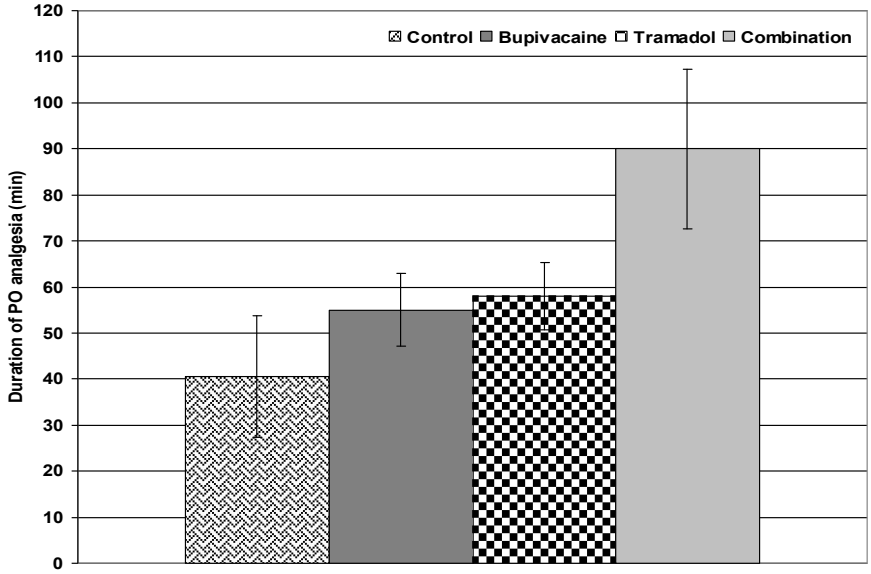

Fig. (2): Mean (±SD) duration of PO analgesia recorded for studied groups

As regards the hospital stay; PACU stay was significantly (p <0.05) shorter in patients received infiltration therapy compared to control group. Moreover, patients received combination therapy stayed in PACU for significantly (p <0.05) shorter duration compared to those received bupivacaine or tramadol with non-significantly (p >0.05) shorter duration in PACU with tramadol compared to bupivacaine. Similarly, total PO hospital stay was significantly (p <0.05) longer in control group compared to other groups, while was significantly (p <0.05) shorter in combination group compared to bupivacaine or tramadol groups with non-significantly (p >0.05) shorter duration with tramadol compared to bupivacaine, (Table 6).

Seventeen patients (21.3%) scored their satisfaction by score=7, 27 patients (33.7%) scored their satisfaction by score=6, 23 patients (28.7%) scored their satisfaction by score=5, 7 patients (8.8%) scored their satisfaction by score=4, 4 patients (5%) scored their satisfaction by score=3 and 2 patients (2.5%) scored their satisfaction by score=2. The frequency of patients showed high satisfaction score was significantly higher in patients received infiltration therapy compared to control group. Combination therapy and tramadol infiltration induced significantly higher satisfaction rates compared to bupivacaine with non-significantly higher satisfaction with combination therapy compared to tramadol alone. Moreover, total satisfaction score was significantly higher in combination group compared to other groups with significantly higher satisfaction scores in bupivacaine and tramadol groups compared to control group, but was non-significantly higher scores with tramadol compared to bupivacaine, (Table 7, Fig. 3).

Table (6): Postoperative hospital stays (hours) data

	PACU stay			Post-PACU stay			Total hospital stay		
	Value	Z	p	Value	Z	p	Value	Z	p
Control	1.1±0.3			8.3±1.9			9.4±1.7		
Bupivacaine	0.8±0.2	3.432	P_1=0.001	6±1.7	3.659	P_1<0.001	6.8±1.7	3.632	P_1<0.001
Tramadol	0.7±0.2	3.558 1.459	P_1<0.001 P_2>0.05	4.5±1.1	3.920 3.846	P_1<0.001 P_2=0.001	5.2±1.1	3.930 3.583	P_1=0.001 P_2=0.003
Combination	0.6±0.1	3.925 3.565 2.388	P_1<0.001 P_2<0.001 P_3=0.017	5.4±1.2	3.420 1.878 2.979	P_1<0.001 P_2>0.05 P_3=0.003	6±1.1	3.932 1.832 2.669	P_1=0.001 P_2>0.05 P_3=0.008

Data are presented as mean±SD; P_1: significance versus Control group, P_2: significance versus Bupivacaine group; P_3: significance versus Tramadol group

Table (7): Patients' distribution according to their satisfaction scores and total scores of studied groups

		Control group	Bupivacaine group	Tramadol group	Combination group
Satisfaction score	7	0	4 (20%)	5 (25%)	8 (40%)
	6	4 (20%)	6 (30%)	9 (45%)	8 (40%)
	5	6 (30%)	8 (40%)	5 (25%)	4 (20%)
	4	4 (20%)	2 (10%)	1 (5%)	0
	3	4 (20%)	0	0	0
	2	2 (10%)	0	0	0
Statistical analysis	X^2		18.446	30.229	65.304
	P_1		<0.001	<0.001	<0.001
	X^2			3.173	9.209
	P_2			<0.05	<0.01
	X^2				2.14
	P_3				>0.05
Total score		4.3±1.3	5.6±0.9	5.9±0.8	6.2±0.8
Statistical analysis	Z		3.862	4.021	3.994
	P_1		<0.001	<0.001	<0.001
	Z			1.730	2.972
	P_2			>0.05	=0.003
	Z				2.449
	P_3				=0.014

Data are presented as mean±SD & numbers, percentages are in parenthesis; P_1: significance versus Control group; P_2: significance versus Bupivacaine group; P_3: significance versus Tramadol group

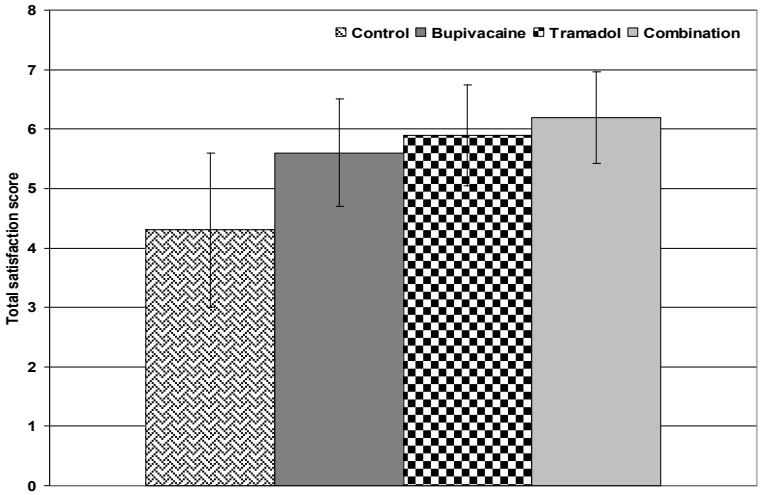

Fig. (3): Mean (±SD) total satisfaction score of studied groups

4. Discussion

Peritonsillar infiltration (PI), irrespective of the medication used provided superior PO analgesia compared to placebo infiltration manifested as significantly longer duration of PO analgesia, lower PO pain scores and consumption of rescue analgesia with shorter hospital stay data. These findings go in hand with that recently reported by **Basuni *et al.* (2013)** who found addition of dexamethasone to levobupivacaine for preoperative PI has better PO analgesic effects than intravenous dexamethasone combined with levobupivacaine PI in children. Also, **Liang *et al.* (2013)** compared lidocaine versus saline PI in adults and found the differences between pain scores were statistically significant.

For comparative purposes, one group received bupivacaine PI alone; in line with this choice, **Sun *et al.* (2010)** performed a meta-analysis to explore the role of perioperative bupivacaine infiltration in the relief of pain in adenotonsillectomy and detected 7 random controlled studies indicated lower pain sensation with lower consumption of rescue analgesia after bupivacaine PI and concluded that bupivacaine PI is a safe and effective method for post-tonsillectomy pain relief. **Ozkiriş *et al.* (2012)** compared ropivacaine versus bupivacaine for peritonsillar analgesia and found ropivacaine infiltration is as effective as bupivacaine for post-tonsillectomy pain management in children.

Concerning the effect of tramadol, tramadol PI alone provided significantly better PO analgesia parameters compared to saline. In line with these data, **Atef & Fawaz (2008)** found tramadol PI appears to be an effective method of providing superior analgesia in the postoperative period when compared to placebo. **Akbay *et al.* (2010)** reported significantly lower pain scores with topical tramadol applied to both tonsillar fossas for 5 minutes and concluded that topical 5% tramadol with its local anesthetic effect seems to be an easy, safe and comfortable approach for pain management after tonsillectomy.

Moreover, tramadol PI alone provided significantly better PO analgesic parameters compared to bupivacaine. In support of the superiority of tramadol versus local anesthesia, **Heiba *et al.* (2012)** found tramadol PI provided pain control in the first 6 hours post-tonsillectomy which was comparable to that of lidocaine. **Ayatollahi *et al.* (2012)** assessed the effect of ketamine and tramadol PI on post-tonsillectomy pain and found preoperative tramadol PI can decrease post-tonsillectomy pain, analgesic consumption, and the time to recovery without significant side effects.

Combined tramadol and bupivacaine PI provided superior analgesic parameters compared to either drug alone. Such effect was in line with that reported for the use of similar combinations for various forms of nerve blocks; **Choudhuri *et al.* (2008)** found caudally administered combined therapy of bupivacaine with either ketamine or tramadol provided significantly longer duration of analgesia without an increase in the adverse effects when compared to bupivacaine alone. **Yildiz *et al.* (2010)** also, found that combination of levobupivacaine and tramadol provided better PO analgesia than that produced by caudal levobupivacaine alone in children. Moreover, **Ozyilmaz *et al.* (2012)** found wound infiltration with combined levobupivacaine and tramadol provided significantly

better analgesia compared with levobupivacaine or tramadol alone.

In line with the use of combined peritonsillar therapy; **Nikandish *et al.* (2008)** reported that PI of combination of bupivacaine and pethidine could significantly decrease the consumption of analgesics for resting pain till 24 h after operation in children undergoing tonsillectomy.

The reported significantly better postoperative analgesic parameters of PI of tramadol compared to bupivacaine signified that both drugs provided analgesia through another local mechanism other than nerve block and despite systemic absorption could occur systemic effect could not be an explanation for such effect. In support of this assumption, pronounced sedation which is the most common side effect of tramadol was not noticed in the studied patients. These data indicated a local analgesic effect of tramadol and supported that previously reported in literature; **Ugur** *et al.* **(2008)** investigated the efficacy of tramadol intramuscular injection and PI to prevent pain in children undergoing tonsillectomy and found tramadol PI provided good intraoperative analgesia, less PO pain on awakening and lower analgesic requirement after surgery.

One of the possible mechanisms for the reported tramadol analgesic effect is its local anesthetic effect, in support of this attribution; **Altunkaya** *et al.* **(2004)** compared the outcome of minor surgical procedures under tramadol or lidocaine subcutaneous infiltration and found the degree of the pain sensation during incision was significantly lower and the time span before taking first analgesic medication was significantly longer in tramadol than lidocaine group and concluded that tramadol can be used as an alternative drug to lidocaine for minor surgeries because of its ability to decrease the demand for postoperative analgesia. **dos Santos** *et al.* **(2010)** reported non-significant difference in the quality of postoperative analgesia after subcutaneous and intravenous tramadol in patients undergoing inguinal herniorrhaphy; despite fewer side effects with subcutaneous injection. **Matkap** *et al.* **(2011)** found trocar site infiltration of tramadol improves early PO pain with significantly longer duration of analgesia, less consumption of PO analgesia, and decreases PO nausea and vomiting compared to IV tramadol.

Secondly, postoperative pain results primarily from direct mechanical damage caused by surgical trauma to the nerve endings. In addition, injury induces the release of a number of endogenous chemical mediators, as serotonin, bradykinin, substance P and histamine, which activate noci-receptors. Prostaglandins facilitate hyperalgesia at the site of surgical trauma by sensitizing noci-receptors to these chemical mediators **(Callesen *et al.*, 1999; Sahbaie *et al.*, 2013)**. Thus, pre-incisional infiltration could ameliorate the release of these nociceptive mediators. This explanation supported that previously experimentally reported by **Bianchi *et al.* (2004)** who reported significant decrease of synovial fluid concentrations of substance P and interleukin-6 after intra-articular injection of tramadol and proposed that tramadol acting as a potential suppressor of the substance P mediated cytokine cascade may be involved in the modulation of inflammatory mediators. **Liu *et al.* (2008)** in a rat model of incisional pain found that tramadol significantly reversed the significantly decreased mechanical thresholds and increased serum interleukin-6 level reported in control group.

4. Conclusion

Pre-incisional peritonsillar infiltration is a safe and effective analgesic modality for post-tonsillectomy pain in adults, irrespective of drug used and the infiltration of combined bupivacaine and tramadol is the appropriate for achieving superior postoperative analgesia.

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8/22/2014