Effect of Tramadol and Ropivacaine Infiltration on Plasma Catecholamine and Postoperative Pain

Mostafa Galal Mostafa[1], Mohamad F. Mohamad[1], Ranya M.Bakry[2] and Waleed S.H.Farrag[*3]

Department of Anesthesia, Intensive Care and pain management[1] Department of Clinical Pathology[2] South Egypt Cancer Institute, Assiut University, [3]Department of Anesthesia and Intensive Care, Medical college, Assiut University. [*]farragwaleed@yahoo.com

Abstract: A long acting local anesthetic; ropivacaine and a synthetic opioid ; tramadol were used to improve pain relief and decrease postoperative systemic analgesic requirement after total thyroidectomy in patients with thyroid cancer. The study also assesses the effect of local infiltration with ropivacaine and tramadol on plasma catecholamine levels. Methods: Ninety six patients underwent thyroid surgery were randomly assigned to 3 groups. Before skin closure, tissues were infiltrated 10 ml of ropivacaine 0.75% plus 5 ml saline in Group R, with 1.5 mg/kg of tramadol in 15 ml saline in Group T, and with 15 ml containing 10 mL ropivacaine 0.75% plus tramadol 1.5mg/kg in Group RT. Plasma epinephrine and nor-epinephrine were recorded at preoperative (0), 1, 5, 15, 30min, 1, 2 and 4 h postoperative. Pain scores at min, 0.1/2, 1,2,4,6, 12, 18, and 24 hr post-operatively; time to first analgesic, number and % of patients requiring rescue analgesia, number of rescue analgesia and total dose of analgesic were recorded. Results; The pain scores in group RT were significantly lower in the first 24 hours than in groups R and T. Time to first analgesic (hrs) in group RT was significantly more than in either group R or group T. The percentage of patients in group RT requiring rescue analgesia was significantly less than the percentage of patients in other groups. Also, the numbers of rescue analgesia requests and the cumulative 24 h analgesic consumption were significantly smaller in group RT than other groups. The plasma epinephrine and nor-epinephrine increased significantly in three groups at 5 and 15 min when compared with the baseline then returned to near baseline value at 30 min 1,2 and 4 hrs. There was significant decrease in plasma concentration of epinephrine and nor-epinephrine in group RT than R or T groups. The aim of this study is to evaluate wound infiltration with ropivacaine, tramadol or their combination on plasma catecholamine levels and post-operative pain following thyroid surgery.

[Mostafa Galal Mostafa, Mohamad F. Mohamad, Ranya M.Bakry[2] and Waleed S.H.Farrag. Effect of Tramadol and Ropivacaine Infiltration on Plasma Catecholamine and Postoperative Pain. Journal of American Science 2011; 7(7): 473-479]. (ISSN: 1545-1003). http://www.americanscience.org.

Key words: Tramadol, Ropivacaine, local infiltration, catecholamine.

1. Introduction:

Post-thyroidectomy pain perception result from peripheral tissue injuries which lead to functional disturbances in the nervous system. There is peripheral sensitization by reducing the threshold of tissue noiception (hyperalgesia) and a central sensitization by increasing the excitability of spinal neurons. These two changes together contribute to the tissue injury pain, which manifests as hypersensitivity state found after peripheral tissue injury (Woolf, 1993). Inhibition of these changes by infiltration of local anesthetic has possible role in prevention of post-operative pain (Woolf, 1989). The primary goals for postoperative analgesia are to provide comfort to the patient with a few side effects as possible, to facilitate the patient's early functional recovery and to decrease length of hospital stay and convalescence. Multiple treatments and techniques have been designed to achieve these goals (Maheshwari et al., 2009). As a result, other analgesic systems have been developed, such as wound infiltration with local anesthetics and analgesics, as well as local anesthetic infiltration through continuous infusion pumps. Recent studies of this technique have obtained promising results, showing a series of advantages for this technique compared with regional techniques or the use of intravenous opioids (Toftdahi et al., 2007). Local anesthetic use can produce analgesic effects through several mechanisms: afferent nociceptor blockade to prevent the transmission of painful nerve impulses, inhibition of inflammatory mediator release, and reduction of free radical and edema formation (Hahnenkamp et al., 2002).

Tramadol, which is a weak opioid, it's analgesic effects are mediated by at least three different mechanisms; it is weak μ opioid receptor agonist, it inhibits the reuptake of the neurotransmitters hydroxytryptamine (5HT) release (Roboux et al., 2004). Previous studies suggest that tramadol possesses some local anesthetic properties when applied to local nerves (Demiraran et al., 2006).

Ropivacine, a long acting amid local anesthetic, is chemically related to bupivacaine but it has less cardiac and central nervous system toxicity (Scott et al., 1989). It produces cutaneous

vasoconstriction that restricts systemic absorption of the drug and increases its local duration of action (Kopacz et al., 1989). Moreover, ropivacaine has anti-inflammatory activity that may further reduce pain when administered locally (Murtinsson et al., 1997). We therefore designed, a prospective, randomized, double-blinded study to compare the effect of infiltration of ropivacaine, tramadol or their combination on plasma catecholamine levels and analgesia efficacy and patient outcome after thyroid cancer surgery.

2. Patients and Methods:

Following approval from the south Egypt Cancer Institute-Assiut University Hospital ethics committee, 96 patients aged 18-50 years, with American Society of Anesthesiology classifications of I and II, undergoing thyroid cancer with block neck dissection under general anesthesia, consented to participate in this randomized, double blinded, clinical trial. Patients with a history of drug dependency, difficulty in communication or a history of allergic reaction to the study drugs, or contraindication to opioids, renal or liver failure, In addition, patients who had previously suffered from a difficult endotracheal intubation (more than two attempts at tracheal intubation) at the induction of anesthesia were also excluded.

Ninety six Patients fifty seven males and thirty nine females were allocated randomly into one of three groups of 32 patients each. Before skin closure, local tissues were infiltrated infiltrated 10 mL of hydrochloride R, ((Naropin; AstraZeneca), with with 1.5 mg/kg of tramad hydrochloride ol in 15 mL saline in Group T (October Pharma S.A.E) and with 15 ml containing 10 mL ropivacaine 0.75% plus tramadol 1.5mg/kg in Group RT.

Using the slandered infiltration technique. Randomization was performed with a computer generated randomization table using sealed envelopes. The anesthesiologist and patient were blinded to the study medicine. A third investigator not involved in the infiltration technique or the assessment of the patient response postoperatively prepared all syringes of the study medications. All patients were pre-medicated with 0.5 mg/ kg of oral midazolam and atropine 0.02 mg kg−1. The same anesthetic technique was used for groups: 1 µg/kg IV fentanyl and 1-2 mg/kg IV propofol as induction agents. Routine monitoring devices (ECG, blood pressure cuff, oxygen saturation monitor and end-tidal CO2) were used. succinylcholine 1 mg kg−1 was used to facilitate tracheal intubation. Anesthesia was maintained with isoflurane and. 0.15 mg/kg IV. Atracurium (0.1mg/kg iv) as a non-depolarizing muscle relaxant.The muscle relaxant effect was reversed at the end of surgery.

In the post anesthesia care unit (PACU), pain was assessed at (0.5,1,2,4,6,8,12,and 24 h)using a visual analogue scale (VAS) which is a psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points (Grant et al., 1999). (VAS) from 0 to 10, with 0 meaning no pain and 10 meaning the worst pain imaginable. Patients requiring rescue analgesia (Paracetamol tab.) was prescribed for patients with a pain score >4. and local reaction(no reaction = 0, mild rash = 1, erythema=2,urticaria=3) and time for first analgesic requirement were recorded.

Plasma catecholamine levels were analyzed by high performance liquid chromatography (HPLC) were measured at 0, 1/2, 15, 30,1,2,4 hrs.

Patients were discharged from the PACU to the ward when they were oriented to time and place, were able to void, and had stable vital signs. Post operative assessment was performed by an investigator, who was unaware of which treatment each patient had received,

Catecholamine Detection:

Plasma catecholamine level was assayed by high performance liquid chromatography (HPLC) with electrochemical detection according to the method of (Nyssonen and Parariainen 1989). The 3, 4-dihydroxyphenyl structure of catecholamine will form cyclic complexes with aluminum oxide, so this property was used in selective pre-purification of catecholamines from biological fluids. A small amount of Alumina is mixed with 3, 4-dihydroxybenzyl amine and TRIS buffer was added.

Vigorous shaking followed by centrifugation was performed then the supernatant was removed and washing with distilled water was done. Diluted HCL was added to extract catecholamines from alumina, these extract was injected into reverse plasma HPLC column, and differences in the molecular structure of the sample molecules determine the attraction of each sample. The column effluent passes through the flow level of an electrochemical detector. The detector oxidizes oxidizable structures and measures the current produced during the transfer of electrons. The current is converted to a voltage signals and sent to an integrator.The detector response to occurs in proposition to the concentration of the analyte.

Statistical analysis:

All statistical analysis was performed using statistical package SPSS for Windows program, version 10.0 .Quantitative data were expressed as mean ±SD or number (%), as appropriate. Qualitative data were analyzed by $\chi 2$ test. Mann-Whitney *U*-test for VAS score. Quantitative data were analyzed by analysis of variance (ANOVA) between groups and by Paired-Student's *t*-test within groups. A value of $P < 0.05$ was considered statistically significant.

3. Results:

As shown in table (1), there were no statistically significant differences among the three groups with respect to age, weight, gender, and duration of surgery.

As shown in table (2), time to First analgesic (h) in group RT was (8.6±0.8) which is significantly more (p□0.05), than in either group R (6.7±0.8) h or group T (6.9.2±0.9) h. The percentage of patients in group RT requiring rescue analgesia was 28%, which is significantly less than the percentage of patients in either group R (90%) or group T (86.7%). Also, the numbers of rescue analgesia requests as well as the cumulative 24 h analgesic consumption were significantly smaller in group RT compared with groups R or T (Table 2).

As shown in fig (1),the VAS score did not differ significantly between tramadol and ropivacaine groups during the 24 postoperative hours, but there was significant difference between ropivacaine and tramadol combination (RT)group and other two groups (P<0.0001).

As shown in fig (2,3), the plasma concentration of epinephrine and nor-epinephrine increased significantly in three groups at 5 and 15 min when compared with the baseline then returned to near baseline value at 30 min 1, 2, 4 h (P<0.001) .There was significant (p□ 0.001) decrease in plasma concentration of epinephrine and nor-epinephrine in group RT than R or T groups.

No significant difference was observed in the incidence of local skin reaction at the injection site. Neither erythema nor urticaria was observed in all groups.

4. Discussion:-

In this study we are able to demonstrate clearly that as compared to infiltration of ropivacaine, tramadol 1.5 mg/kg and their combination after the surgical incision visibly improves post operative pain. Among those three groups who received infiltration of local anesthetic fewer analgesic requests , the time for the first analgesic request, number and % of patients requiring rescue analgesia and total consumption of analgesic medications was significantly little in combination group. This fact provides evidence that group of patients had better analgesic conditions and this confirmed by our clinical observation but in group tramadol and group ropivacaine these parameters lie in the same statistical range.

Table (1): Demographic characteristics, and surgical data of patients (Values are number (n) or M ± SD)

Variable	Group R (n = 32)	Group T (n = 32)	Group RT (n = 32)	*P-value*
Age (yr)	51 ± 16	49 ± 15	46 ± 14	0.139
Weight (kg)	76 ± 17	78 ± 19	75 ± 16	0.091
Gender (female/male)	19 / 13	20 / 12	18 / 14	0.878
Duration of anesthesia (min)	163 ± 33	166 ± 34	168 ± 35	0.471
Duration of operation (min)	148 ± 30	150 ± 30	152 ± 31	0.379

Table (2): Postoperative Quality of Analgesia (mean ± SD)

Variable	Group R (n = 32)	Group T (n = 32)	Group RT (n = 32)	*P-value*		
				R vs. T	*R vs. RT*	*T vs. RT*
Time to First analgesic (h)	6.7 ± 0.8	6.9.2 ± 0.9	8.6 ± 0.8	0.804	0.054	0.079
No. and % of patients requiring rescue analgesia (Paracetamol)·	29 (90%)	28 (86.7%)	9 (28%)	0.689	0.001*	0.001*
No. of rescue analgesia	1.7 ± 1.0	1.4 ± 0.8	0.4 ± 0.6	0.190	0.001*	0.004*
Total dose (no. of tablets/24 h)	3.3 ± 1.9	2.7 ± 1.6	0.8 ± 1.3	0.177	0.001*	0.001*

*p□ 0.05

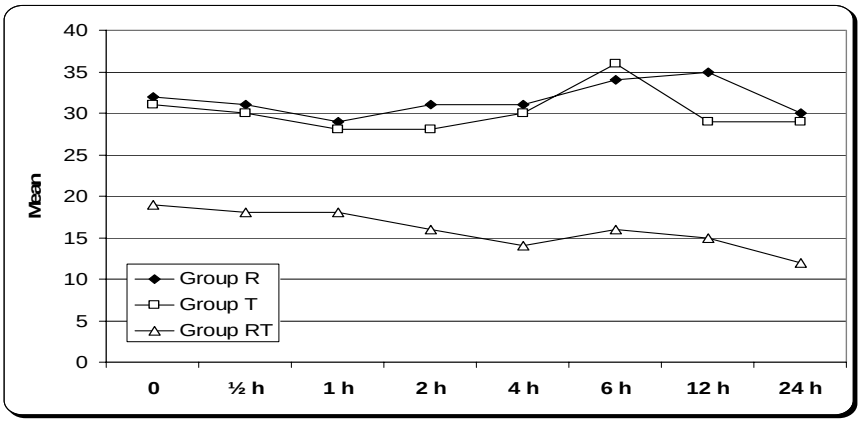
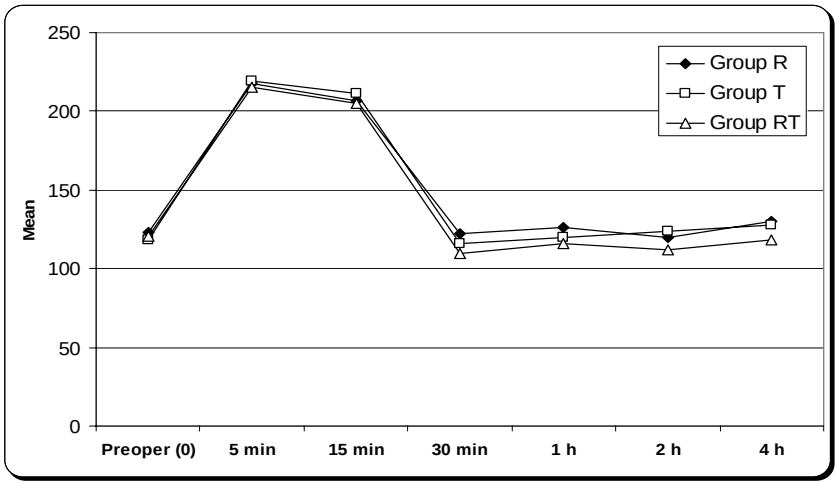
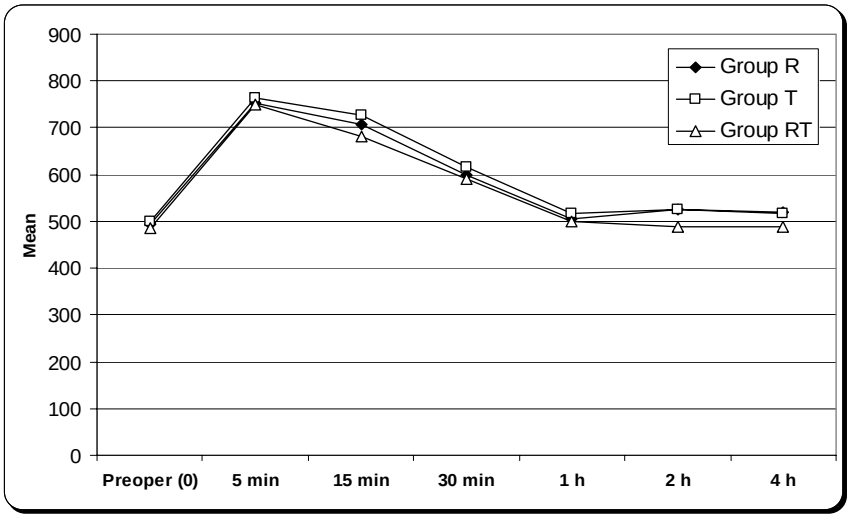


Fig (1): Visual Analog Scores (VAS) as Mean ± SD at different time intervals following operations



Fig(2):Time course of changes in the plasma epinephrine after drugs infiltration



Fig(3):Time course of changes in the plasma nor epinephrine after drugs infiltration

Non-steroidal anti-inflammatory drugs used in, decreasing pain and opioid requirements but in some patients may be limited by adverse renal, gastrointestinal, and hematological (Kam and Power, 2000). Also opioids can be used, although highly effective in managing pain have a range of side effects such as respiratory depression, sedation, nausea, and vomiting (Fishman and Borsook, 1999), so we are used local anesthetics infiltration as alternative method.

Post-thyroidectomy pain perception likely includes components linked to the deep and superficial layers of the wound, intra operative neck position and wound and drainage and this pain may be treated with NSAIDs or opioids (Dieudonne etal., 2001).

Infiltration with local anesthetic at operative sites can improve postoperative analgesia and reduce opioid requirements after different surgical procedures (Bianconi et al., 2003).

Postoperative analgesia using wound infiltration with ropivacaine 3.75% or 7.5% leads to a significant reduction of VAS values and opioid consumption in patients undergoing major shoulder surgery (Horn et al., 1999).

Ropivacaine (70ml of 0.25%) infiltrated into cholecystectomy wound significantly decreases wound pain and increases the time to the first request for post operative analgesia compared with saline (Johansson et al.,1994).

Wound infiltration with 0.25%ropivacaine or bupivacaine 40ml was equally effective in the management of post- herniorrhaphy pain (Erichsenet et al., 1995).

Ropivacaine produces vasoconstriction thus, it can provide further analgesic advantages (Burmester et al., 2005).

Local anesthetic wound infiltration with abdominal hysterectomy does not decrease post-operative opioid requirements or improve patient comfort (Klein et al., 2000 and Cobby and Reid, 1997).

Bupivacaine infiltration in thyroid surgery markedly reduced opioid requirements (Gozal et al., 1994).

Bupivacaine wound infiltration effectiveness was considered disappointing when compared with two opioid regimens (Lacoste et al., 1997).

In our study, we found that local wound infiltration with tramadol (1.5mg .kg) and ropivacaine combination prior to wound closure in thyroidectomy provided significant post operative analgesia and delayed onset of postoperative pain (8.6±0.8, 6.7±.08, 6.9±0.9) hours respectively when compared to ropivacaine or tramadol with no significant side effects in this set of patients and this regional analgesic effect may due to a multimodal mechanismof action, which gives a synergistic effect.

Tramadol possesses some local anesthetic properties when applied to peripheral nerves (Houmes et al., 1992).

A dose of 100 mg tramadol added to 40 mL of 1.5% mepivacaine improved the quality of the brachial plexus blockade in patients scheduled for forearm and hand surgery (Robaux et al., 2004).

Tramadol (2mg/kg) has a local anesthetic effects with minimal sedation and cardiovascular compromise (Demiraran et al., 2006).

Subcutaneous tramadol infiltration can provide effective analgesia and anti-inflammatory effects (Grecek et al., 2004).

Tramadol exerts its sensory blocking action by a mechanism similar to that of local anesthetics (Jou et al., 2003).

Subcutaneous 2 mg/kg tramadol had a local anesthetic action similar to 1mg/kg lidocaine and they correlated that to its antinocicceptive effect, which might be extended into the post-operative period (Alunkaya et al., 2004).

Tramadol is structurally related to codeine, which is, in fact, a methyl-morphine, so tramadol exerts its action on central monoaminergic systems and this mechanism may contribute to its analgesic effect (Shipton, 2000).

The duration of postoperative analgesia provided by subcutaneous tramadol was significantly longer compared with lidocaine (group 4.9 ± 0.3, group L 4.4 ± 0.7 h) (Alunkaya et al., 2003).

Tramadol, added to mepivacaine for brachial plexus anesthesia, extend the duration and improve the quality of postoperative analgesia (Robaux et al. 2004).

Postoperative analgesia was significantly prolonged and fewer analgesics were required after wound infiltration with tramadol (2mg/kg) and this technique may be a good choice for postoperative analgesia in children having inguinal hernia repair (Demiraran et al., 2006).

Tramadol 100 mg intraarticular without local anesthesia provided lower VAS pain scores and longer analgesic effect more than after IV injection of the same doses with no significant side effects (Alagol et al., 2004).

In this study we found that local wound infiltration with tramadol (1.5mg .kg) and ropivacaine prior to wound closure in thyroidectomy provided nearly equal post operative analgesia and delayed onset of postoperative pain may be due to vasoconstriction of ropivacaine or action of tramadol on both opioid and non-opioid systems.

A smaller dose of tramadol (1 mg/kg) among adult post herniorrhaphy patients achieved the same

analgesic time (6.6±0.9) hours and this was agreement with our study (group T 6.9±0.9 hours) (Abdullah et al., 2008).

Subcutaneous wound infiltration with tramadol reduces postoperative opioid consumption and produces less nausea and vomiting than the intravenous administration after pyelolithotomy (Khajavi et al., 2009).

Our data indicate that wound infiltration with either ropivacaine 0.75% or tramadol hydrochloride or their combination produced an elevation in the plasma epinephrine and nor-epinephrine at 5 and 15 min and this elevation may be due to surgical stress or sympatho-adrenal response and return nearly to baseline at 30 min 1,2 4 h and there was significant decrease in plasma concentration of epinephrine and nor-epinephrine in group RT than R or T and this may be due to synergistic effect of the combination of the two drug infiltration or intra-operative fentanyl.

Injection of local anesthetic containing epinephrine resulted in an increase in plasma epinephrine level that is associated with cardiovascular changes (Dionne et al., 1984).

Nor-epinephrine is an endogenous catecholamine and is useful as an indicator of a patient's stress response (Lake et al., 1976).

Epidural ropivacaine 0.75% is more effective for the purpose of controlling surgical stress (catecholamine responses) than 0.375% under the same general anesthesia (Shinhe et al., 2004).

Tramadol inhibits catecholamine secretion at least partly by inhibiting nicotinic AChR functions at clinically relevant concentrations in a manner independent of opioid receptors and this inhibitory effects of tramadol on nicotinic AChR functions might be one of the antinociceptive mechanisms exerted by tramadol (Shiraishi et al., 2002).

In the present study no significant difference was observed in the incidence of local skin reaction at the injection site , neither erythema nor urticaria was observed in all groups and this was agreement with Kargi et al. when used tramadol for local infiltration analgesia without any local side effects.

Tramadol in IVRA it resulted in a skin rash distal to the tourniquet, suggesting histamine release (Acalovschi et al., 2001).

found that the incidence of painful or burning sensations at the intradermal injection site and local reactions (i.e. rash) were significantly greater in tramadol-treated than prilocaine-treated patients (Alunkaya et al., 2003).

In conclusion, Wound infiltration with ropivacaine 0.75% plus tramadol 1.5mg/kg combination produces the least percentage of increase in the plasma epinephrine and nor epinephrine and improves postoperative pain control and patient comfort, and decreased the need for opioids than the use of either drug alone.

Corresponding author
Waleed S.H.Farrag
Department of Anesthesia and Intensive Care, Medical College, Assiut University.
farragwaleed@yahoo.com

References:-

1- Abdullah M. Kaki and Waleed Al Marakb. 2008: Post-herniorrhaphy infiltration of tramadol versus bupivacaine for postoperative pain relief: a randomized study. Ann Saudi Med; 28(3): 165-168.
2- Acalovschi I, Cristea T and Margarit S. 2001: Tramadol added to lidocaine for intravenous regional anesthesia. Anesth Analg; 92: 209.
3- Acalovschi I, Cristea T, Margarit S. 2001: Tramadol added to lidocaine for intravenous regional anesthesia.Anesth Analg; 92: 209– 214.
4- Alagol A, Calpur OU, Kaya G, Pamukcu Z and Turan FN. 2004: The use of intraarticular tramadol for postoperative analgesia after arthroscopic knee surgery: a comparison of different intraarticular and intravenous doses. Knee Surg Sports Traumatol Arthrosc; 12:184–8.
5- Alunkaya H,Ozer Y and Kargi E. 2004: The postoperative analgesic effect of tramadol when used as a subcutaneous local anesthetic . . Aneth Analg; 99:1461-1464
6- Bianconi M, Ferraro L and Traina GC. 2003: .Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery.Br J Anaesth; 91: 830–5.
7- Burmester MD,Schluter KD and Daut J. 2005: Enantioselective actions of bupivacaine and ropivacaine on coronary vascular resistance at cardiotoxic concentrations. Anesthes Analg; 100:707-12.
8- Cobby TF and Reid MF. 1997: Wound infiltration with local anesthetic after abdominal hysterectomy.Br J Anaesth; 78: 431–2.
9- Daou R. 1997: Thyroidectomy without drainage.Chirurgie; 122: 408–10.
10- Demiranan Y, Lica Z and Kocaman B. 2006: Does tramadol wound infiltration offer an advantage over bupivacaine for postoperative analgesia in children following tonsillectomy. Pediat Anesth; 16: 1047-1050.
11- Demiraran Y, Ilce Z and Kocaman B. 2006: Does tramadol wound infiltration offer an advantage over bupivacaine for postoperative analgesia in children following herniotomy? Pediatr Anaesth; 16(100):1047-50.
12- Dieudonne N, Gomola A, Bonnichon P and Ozier YM. 2001: Prevention of postoperative pain after thyroid surgery: a double-blind randomized study of bilateral superficial cervical plexus blocks.Anesth Analg; 92: 1538– 42.
13- Dionne RA, Goldstein DS and Wirdzek PR. 1984: Effect of of diazepam premedication and epinepherine-

containing local anethetic on cardiovascular and plasma catecholamine responses to oral surgery.Aneth Analg;63:640-646
14- Erichsen CJ,Vibits H and Dahl JB. 1995: Wound infiltration with ropivacaine and bupivacaine for pain after inguinal herniotomy.Acta Anethesthesiologica Scandinavica; 39:67-70.
15- Fishman S, Borsook D. Benzon H, Raja S, Molloy RE and Strichartz G. 1999: Essentials of Pain Medicine and Regional Anesthesia. New York: Churchill Livingstone;: 51–4.
16- Gercek A, Eti Z and Gogus FY. 2004: The analgesic and anti-inflammatory effect of subcutaneous bupivicaine, morphine and tramadol in rats. Agri; 16:53-58.
17- Gozal Y, Shapira SC, Gozal D and Magora F. 1994: Bupivacain wound infiltration in thyroid surgery reduces postoperative pain and opioid demand. Acta Anaesthesiol Scand; 38: 813–5.
18- Grant S, Aitchinson T, Henderson E, Christin J, Zare S and Dargie H.1999: A comparison of the reproductibility and the sensitivity to change of visual analogue scales, borg scales and likerts scales in normal subjects during submaximal exercise. Chest; 10: 116-137.
19- Hannenkamp k, Theilmaier G, Aleen HK, Hoenemann CW. 2002: The effects of local anesthetic on perioperative coagulation, inflammatory and microcirculation. Anesth Analg; 94: 1441-1447.
20- Horn EP, Schroeder F and Wilhelm S. 1999: Wound infiltration and drain lavage with ropivacaine after major shoulder surgery.Anesth Analg; 89: 1461–6.
21- Houmes R, Voets MA and Verkaaik A. 1992: Effficacy and safety of tramadol versus morphine for moderate and severe postoperative pain regarding respiratory depression.Anesth Analg; 74:510-514.
22- Johansson B, Glise H and Haaerback B. 1994: Preoperative local infiltration with ropivacaine for postoperative pain relief after cholecystectomy.Anesthesis and Analgesia; 78:210-214.
23- Jou IM, Chu KS and Chen HH. 2003: The effect of intrathecal tramadol on spinal somatosensory evoked potentials and motor evoked responses in rats. Anesth Analg; 96:783-8
24- Kam PC and Power I. 2000: New selective COX-2 inhibitors Pain Reviews; 7: 3–13.
25- Khajavi MR, Aghili SB, Moharari RS, Najafi A, Mohtaram R, Khashayar P and Mojtahedzade M. 2009: Subcutaneous tramadol infiltration at the wound site versus intravenous administration after pyelolithotomy. Ann Pharmacother. Mar; 43(3):430-5. Epub 2009 Mar 3.
26- Klein JR, Heaton JP, Thompson JP, Cotton BR, Davidson AC and Smith G. 2000: Infiltration of the abdominal wall with local anesthetic after total abdominal hysterectomy has no opioid-sparing effect. Br J Anaesth; 84: 248–9.
27- Kopacz DJ, Carpenter RL and Mackey DC. 1989: Effect of ropivacaine on cutaneous capillary blood flow in pigs.Anesthesiology; 71: 69–74.
28- Lacoste L, Thomas D and Kraimps JL. 1997: Postthyroidectomy analgesia: morphine, buprenorphine, or bupivacaine?J Clin Anesth; 9: 189–93.
29- Lake C,ziegler MG and Kopin JJ. 1976: Use of plasma norepinepherine for elevation of symppathetic neuronl function in man.Life Sci;18 :1315-1325.
30- Maheshwari .V, Blum Y.C, Sherkhart L, Ranawat .S. 2009: Multimodel pain management after total knee arthroplasty. Clin Ortho Res;67: 1418-1423.
31- Martinsson T, Oda T, Fernvik E, Roempke K, Dalsgaard CJ and Svensjo E. 1997: Ropivacaine inhibits leukocyte rolling,adhesion and CD11b/CD18 expression.J Pharmacol Exp Ther; 283: 59–65.
32- Nyssonen K and Parariainen M. 1997: Plasma Catecholamines: Laboratory Aspects, Critical Reviews.Clinical Laboratory Sciences 1989;27:211-236
33- Robaux S, Blunt C and Veil E. 2004: Tramadol addedto 1.5% mepivicaine for axillary brachial plexus block improves postoperative analgesia dose dependently. Anesth Analg; 98:1172-117.
34- Roubaux S, Blunt C and Veil E. 2004: Tramadol added to 1.5%mepivacaine for axillary brachial plexus block improve postoperative analgesia dose-dependentel. Anesth Analg; 98: 1172-1177.
35- Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P and Lundh R. 1989: Acute toxicity of ropivacaine compared with that of bupivacaine.Anesth Analg; 69: 563–9.
36- Shinhe Lee, Tetsuro Nikai, Katsushi Doi, Shinichi Sakura and Yoji Saito. 2004: Surgical Stress Response during Combined General/Epidural Anesthesia for Upper Abdominal Surgery: Comparison of 0.375% and 0.75% Ropivacaine. Anesthesiology; 101: A921.
37- Shipton EA. 2000: Tramadol: present and future. Anesth Intensive Care; 28:363–74.
38- Shiraishi M, Minami K, Uezono Y, Yanagihara N, Shigematsu A and Shibuya I. 2002: Inhibitory effects of tramadol on nicotinic acetylcholine receptors in adrenal chroma n cells and in Xenopus oocytes expressing a7 receptors.British Journal of Pharmacology 136, 207 ± 216.
39- Toftdai K, Nikolajsen L, Haraldsted V, Madsen F, Tonnesan EK, Soballe K. 2007: Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty; a randomized clinical trial. Acta Ortho; 78: 172-179.
40- Woolf C J. 1989: Recent advances in the pathophysiology of acute pain. Br J Anesth, 63: 139-46
41- Woolf C J. 1993: Preemptive analgesia treating post operative pain by preventing the establishment of central sensitization. Anesth Analg; 362 - 79