Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(5) (Part - I): 1627-1634
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6519.21

Comparison between Ropivacaine and Ropivacaine Plus Tramodol in Wound Infiltration as an Analgesic after Open Cholecystectomy Surgeries for Post-operative Analgesia

Saurin B Panchal[1], Vatsal C Patel[2], Tarak K Modi[3]

[1]Assistant Professor, [3]Resident Doctor, Department of Anesthesia, Smt SCL Hospital, NHL Medical College, Ahmedabad, Gujarat 380006, India. [2]Assistant Professor, Department of Anesthesia, VS Hospital, NHL Medical College, Ahmedabad, Gujarat 380006, India.

Abstract

Post-operative pain is common after abdominal surgery and is a major cause of patient dissatisfaction in post-operative period. Various drugs like opioids, nonsteroidal anti-inflammatory drugs, dexamethasone has been used to control post-operative pain but efficacy is variable. Wound infiltration is being used now-a-days to provide analgesia in immediate post-operative period. Ropivacaine, a newer longer acting local anesthetic, is used due to its less side effects. Tramadol can be used to as an adjuvant to ropivacaine in wound infiltration. A total of 75 patients, posted for open cholecystectomy, were randomly divided into three groups. Group C – inj. normal saline *22 ml*, Group R- 0.375% ropivacaine *20 ml* + inj. normal saline *2 ml*. Group RT- 0.375% ropivacaine *20 ml* + inj. tramadol *2 mg/kg* in *2 ml*. A total volume of *22 ml* was infiltrated. Local wound infiltration was done at time of closure according to study groups.VAS score in post-operative period, time for first rescue analgesic, number of rescue doses in first *24 hrs*, PONV and patient satisfaction were noted. There was higher VAS score and early requirement of rescue dose in control group compared to group R and RT ($p < 0.001$). There was also longer duration of analgesia in group RT compared to group R ($p < 0.05$). Incidences of PONV were comparable in all three groups. Ropivacaine and ropivacaine-tramodol were effective in wound infiltration for post-operative analgesia but later was preferred due to longer duration of action and better patient satisfaction without increased incidence of PONV.

Keywords: Infiltration; Ropivacaine; Tramadol.

How to cite this article:

Saurin B Panchal, Vatsal C Patel, Tarak K Modi *et al.* Comparison between Ropivacaine and Ropivacaine Plus Tramodol in Wound Infiltration as an Analgesic after Open Cholecystectomy Surgeries for Post-operative Analgesia. Indian J Anesth Analg. 2019;6(5 Part-1): 1627-1634.

Introduction

Post-operative pain is inevitable after major upper abdominal surgeries like open cholecystectomy. Post-operative pain may cause stress response to body and respiratory or cardiac complications.[1–3] So, post-operative pain should be controlled as early as possible.

Post-operative analgesia is important part of optimal peri-operative management. Currently various methods are available for post-operative pain control like epidural analgesia, intravenous analgesia and patient controlled analgesia pump.[4] Opioids are mainstay of post-operative pain control but are associated with some adverse side effects like respiratory depression, sedation, nausea

Corresponding Author: Saurin B Panchal, Assistant Professor, Department of Anesthesia, Smt SCL Hospital, NHL Medical College, Ahmedabad, Gujarat, India.

E-mail: drsaurin01111987@gmail.com

Received on 11.06.2019, **Accepted on** 24.07.2019

and vomiting.[5–7] Nonsteroidal anti-inflammatory drugs are less effective as sole analgesic after upper abdominal surgeries. Local anesthetic methods are more useful than intravenous analgesia with less side effects irrespective of surgical procedure.[8]

Now-a-days, wound infiltration with local anesthetic drugs is widely used in various surgeries as a part of optimal post-operative pain control.[9,10] Wound infiltration is safe, effective and inexpensive method of post-operative pain control. It provides immediate analgesia lasting for few hours without major side effects.[11,12]

Bupivacaine and ropivacaine are commonly used local anesthetics in wound infiltration due to longer duration of action.[13] Ropivacine has wider safety profile and associated with less adverse events. 0.375% and 0.5% concentrations of ropivacaine are commonly used for wound infiltration for post-operative analgesia.[14,15] Various adjuvants are used in addition to local anesthetics to potentiate effects of local anesthetics and reduce rescue analgesic requirement.[5,16,17]

Tramadol is commonly used in wound infiltration due to its safety and efficacy. Tramadol is weak opioid and its local anesthetic effects have been demonstrated in various studies.[18] As an adjuvant in wound infiltration, tramadol can potentiate effects of local anesthetics without systemic side effects.[13] Tramadol has less potential for respiratory depression and abuse unlike other commonly used opioids.[19]

Aims

Aim of our study was to compare effectiveness of wound infiltration with ropivacaine alone and ropivacaine plus tramodol after open cholecystectomy surgeries in term of post-operative analgesia. Secondary outcomes measured were time for first rescue analgesic, number of rescue doses in first *24 hrs*, patient satisfaction and side effects if any.

Materials and Methods

This prospective randomized double blind study was carried out in our institute from Nov 2018 to March 2019. A total of 75 patients of age group *20–50 years*, either gender, belonging to ASA I/II posted for elective open cholecystectomy surgeries were selected in our study. Written informed consent was taken from each patient. Patients were divided into three groups, 25 patients in each group.

Exclusion Criteria

- Patient refusal
- Allergy to local anesthetic drugs
- Liver dysfunction
- Renal dysfunction
- History of treatment on pain medications or opioids use
- Severe un-controlled comorbities like diabetes, hypertension
- Bleeding disorders

Meticulous pre-operative evaluation was carried out on day before surgery. Visual Analogue Score (VAS) was used to grade intensity of pain in post-operative period. Patients were given information about VAS score grading pre-operatively. VAS is pain measurement tool ranging from 0 to 10, 0-no pain, 10-most severe pain. All patients were premedicated with inj. gycopyrrolate *4 mcg/kg* and inj. midazolam *1 mg* intravenous *30 minutes* before surgery. All patients were induced with general anesthesia. All patients of three groups were induced with inj. sodium pentothal *6 mg/kg* and inj. succinylcholine *1.5 mg/kg*. All patients were given inj. fentanyl *1.5 mcg/kg*. Anesthesia was maintained with oxygen, sevofluarne 1 MAC and inj. atracurium. At time of wound closure, muscle, subcutaneous tissue and skin infiltration were carried out by operating surgeon with total volume of *22 ml* according to study group. Randomization was done with sealed envelope technique.

Group C – Inj. Normal saline (0.9%) - Total volume *22 ml*;

Group R – Inj. Ropivacaine (0.375%) *20 ml* + Inj. Normal saline *2 ml* - Total volume *22 ml*;

Group RT – Inj. Ropivacaine (0.375%) *20 ml* + Inj. Tramadol (*2 mg/kg*) in *2 ml*-Total volume *22 ml*.

At the end of surgery, patients were reversed from neuromuscular blockade with inj. glycopyrrolate *8 mcg/kg* and inj. neostigmine *0.05 mg/kg*. Hemodynamic parameters were recorded intra-operatively and immediate post-operative period upto *24 hrs*. Post-operative pain was measured using VAS score in immediate post-operative period, *30 min*, *1 hr*, *2 hr*, *4 hr*, *6 hr*, *8 hr*, *12 hr*, *18 hr* and *24 hr*. VAS score > 3 at anytime was noted and rescue drug in form of inj. diclofenac *1.5 mg/kg* I.V. slowly was given. VAS score at different time interval and time for first rescue analgesic were recorded. Number of rescue doses in first *24 hrs* in post-operative period and incidences of post-operative nausea/vomiting were also recorded.

Patient satisfaction score at 24 hr was also recorded using patient satisfaction scale (0–4), 0-poor to 4-excellent. Operating surgeons whose had done infiltration and anesthesiologists taking follow up in post-operative period were kept blind to study drug administered.

Statistical Analysis

All data were collected and analysed with SPSS 17 software. Statistical methods such as Anova test, student's *t*-test and chi-square test were performed to find level of significance of our data values for all three groups. Level of significance was set to $p < 0.05$.

Results

All 75 patients of three groups were assessed and results were shown in (**Tables 1–5**).

Table 1: Demographic characteristics

	Group C	Group R	Group RT	*p* value
Age	34.56 ± 12.35	33.38 ± 10.79	36.78 ± 12.88	> 0.05
Sex (M/F)	20:5	18:7	21:4	> 0.05
ASA I/II	24/1	23/2	24/1	> 0.05
Weight	62.10 ± 11.67	66.45 ± 13.01	63.78 ± 15.89	> 0.05
Duration of surgery	81.78 ± 16.68	85.98 ± 13.85	84.87 ± 14.37	> 0.05

All patients of three groups were comparable in demographic profiles, ASA status and duration of surgery ($p > 0.05$) (Table 1).

There was no difference in VAS score till post-operative period *1 hr* for all three groups. There was significant increase in VAS score around *1 hr* in Group C, difference is statistically significant ($p < 0.05$). VAS score were comparable in Group R and Group RT during all times except *4 hr*, *6 hr* and *8 hr*, ($p > 0.05$) (Table 2).

Time for first rescue analgesic was significant shorter in Group C compared to other two groups ($p < 0.05$). There was also significant difference in time for first rescue analgesic for Group R and Group RT, shorter in group R ($p < 0.05$). Number of rescue doses requirement in first *24 hrs* was highest for Group C and least for Group RT, difference is statistically significant, ($p < 0.05$) (Table 3).

Table 4: PONV incidence

	Group C	Group R	Group RT	*P* value
Nausea/vomiting (First *24 hrs*)	5 (20%)	4 (16%)	5 (20%)	> 0.05

There was no significant difference in incidences of PONV in first *24 hrs* for all three groups ($p > 0.05$) (Table 4).

Table 5: Patient satisfaction scale

	Group C	Group R	Group RT	*p* value
Patient satisfaction scale (At *24 hrs*)	1.56 ± 0.56	2.05 ± 0.57	2.89 ± 0.67	< 0.05

Patient satisfaction at *24 hrs* was higher with group R and RT compared to Group C. There was significant difference for level of patient satisfaction for Group R and RT, higher satisfaction with Group RT ($p < 0.05$) (Table 5).

Table 2: VAS score in post-operative period

	0 *min*	30 *min*	1 *Hr*	2 *Hr*	4 *Hr*	6 *Hr*	8 *Hr*	12 *Hr*	18 *Hr*	24 *Hr*
Group C	2.06 ± 0.34	2.17 ± 0.34	2.67 ± 0.98	2.00 ± 0.37	2.10 ± 0.43	2.64 ± 0.83	2.20 ± 0.54	2.35 ± 0.46	2.43 ± 0.77	2.39 ± 0.33
Group R	1.78 ± 0.34	2.10 ± 0.67	2.14 ± 0.56	2.30 ± 0.45	2.89 ± 1.23	2.11 ± 0.87	2.08 ± 0.65	2.34 ± 0.54	2.53 ± 0.56	2.26 ± 0.34
Group RT	1.89 ± 0.56	2.30 ± 0.45	2.27 ± 0.56	2.10 ± 0.66	2.76 ± 0.97	2.23 ± 0.65	2.63 ± 0.64	2.23 ± 0.54	2.50 ± 0.87	2.13 ± 0.31

Table 3: Post-operative rescue dose requirement

	Group C	Group R	Group RT	*p* value
Time for first rescue dose	56.23 ± 16.67	280.78 ± 40.67	400.65 ± 50.34	< 0.001(C & R) < 0.001(C& RT) < 0.01 (R & RT)
Number of rescue doses in *24 hrs*	2.45 ± 0.78	1.46 ± 0.75	1.03 ± 0.65	< 0.001(C & R) < 0.001(C& RT) < 0.03 (R & RT)

Discussion

Pain is a protective body mechanism to injurious stimulus with or without actual tissue damage.[20] Individual variations in response to pain may be influenced by age, gender, genetic makeup and site of surgery.[21,22] Approximately 80–90% surgical patients experience moderate to severe pain post-operatively.[23,24] Post-operative pain due to surgical incision is nociceptive acute pain which is major cause of post-operative morbidity.

In-adequate control of post-operative pain has certain adverse health impacts on cardiovascular and respiratory system, like hypertension, tachycardia, in-adequate coughing, basal atelectasis, deep vein thrombosis, insomnia. Besides this, it delays early ambulation and prolong hospital stay.[25,26] Post-operative pain may be major cause of patient dissatisfaction after surgery. So, efforts should be always towards early and effective control of post-operative pain.

Management of post-operative pain is challenging after abdominal surgeries. Effective post-operative pain control can provide faster recovery, early hospital discharge and better patient satisfaction.[27]

Appropiate methods should be applied as early as possible to control pain in immediate post-operative period. Various drugs like, opioids and nonopioids drugs has been used to effectively control post-operative pain. Opioids are cornerstone for post-operative pain control. Morphine, fentanyl, sufentanyl are effective for moderate to severe post-operative pain. These drugs are associated with some side effects like respiratory depression, pruritus, urinary retention, nausea and vomiting which may cause patient discomfort.[5–7,28]

Nonsteroidal anti-inflammatory drugs like paracetamol, diclofenac, ketorolac are commonly used as second line drugs for post-operative pain control. These drugs are in-effective as sole analgesic after abdominal surgeries. As these drugs are less effective for moderate to severe pain which is common in immediate post-operative period.[8,28] They can be used as part of multimodal approach.

However, post-operative pain control is still demanding in first *24 hrs*. No single available method is effective for optimal post-operative pain control. Post-operative pain should be controlled effectively at earliest by multimodal approach so side effects of individual drugs could be minimized.[5] American society of anesthesiologists also stated that acute pain might be better controlled with multimodal analgesia.[29]

Wound infiltration is important part of a multimodal approach for post-operative analgesia. Local wound infiltration is attractive method as it is simple, effective and side effects are minimal.[3,30] Various studies have shown that incisional infiltration of local anesthetics was safe and effective technique for post-operative pain relief in orthopedic surgeries, abdominal surgeries and cesarean sections.[18,31–35] So we had chosen local anesthetics wound infiltration method for post-operative analgesia in open cholecystectomy surgeries.

Various local anesthetics, like bupivacaine and ropivacaine, are used in wound infiltration in various surgeries like open cholecystectomy. Local anesthetics used in wound infiltration block afferent pain signals from incision site and reduce sensitization of spinal dorsal horn neurons.[36,37] Local anesthetics can inhibit sensitization of nociceptive receptors that can cause in-flammatory response. Various studies have shown that infiltration with local anesthetics may reduce interleukin levels and increase substance *P* in the wound.[19]

Ropivacaine, longer acting anesthetic, has been widely used in local wound infiltration besides its use peripheral nerve blocks and epidural anesthesia. Ropivacaine is nearly comparabale to bupivacaine in terms of potency and duration of action with better safety profile.[5,38] Ropivacaine is less lipophilic hence less chances of central nervous system and cardiovascular toxicity.[14,15,17] Various studies have shown that 0.375% and 0.5% ropivacaine could be used for local wound infiltration, with maximum dose being *3 mg/kg*.[13,14,17,39] So, we had used 0.375 % ropivacaine in wound infiltration for post-operative analgesia.

Wound infiltration with local anesthetics has short duration of action (*30 min* to *6 hr*) even with longer acting anesthetic ropivacaine.[14] Despite use of longer acting ropivacaine, there is always need for adjuvants to prolong duration of analgesia. With single shot wound infiltration, duration of analgesia is more limited as catheter may have certain disadvantages like dislodgement and infection.[31] Various additives had been used to local anesthetic infiltration to improve quality and duration of post-operative analgesia. Tramadol, fentanyl, morphine, sodium bicarbonate and dexmedetomidine are commonly used as additive to local anesthetics in wound infiltration.[40–42]

Various studies has shown that infiltration with opioids could potentiate analgesic action of local anesthetics in wound infiltration.[40,41] As an adjuvant, tramadol is gaining popularity in wound

infiltration besides systemic use for pain control. Tramadol is a synthetic opioid used as an adjuvant to local anesthetic in wound infiltration. It may exerts its analgesic effects through μ receptors and inhibition of monoaminergic transmitters. Various studies has demonstrated that tramadol might had anti-inflammatory and local anesthetic action on peripheral nerves.[43–46] Various studies has shown that tramadol in dose of *1.5–2 mg/kg* could be effective in wound infiltration for post-operative analgesia.[19,39,47,48] So, in our study, we had used tramadol in dose of *2 mg/kg* for infiltration in open cholecystectomy surgeries.

Wound infiltration volume may depend on length of surgical incision. Various studies have shown that volume used for wound infiltration for post-operative analgesia could range from *20 ml–40 ml* depending on nature of surgery.[5,12,13,17,32,39] So. we had used total volume of *22 ml* in open cholecystecomy wound infiltration for post-operative pain control.

In our study, we found that VAS scores were significantly higher in control group (Group C) compared to other groups. These findings were indicating that wound infiltration with local anesthetic drugs might reduced pain score by providing post-operative analgesia. Duration of pain relief of wound infiltration with ropivacaine was comparable to that reported by study of Baudry *et al.*[49]Axelle V *et al.* also demonstrated that wound infiltration with ropivacaine after breast cancer surgery had lower pain score compared to control group during immediate post-operative period.[12] Jing Xian *et al.* also revealed that wound infiltration with ropivacaine after open hepatectomy decresed VAS score compared to saline group. These findings correlated with our study.[3]

VAS scores were also higher in ropivacaine group compared to ropivacaine-tramodol group. These findings were indicative of efficacy of tramodol as an adjuvant to ropivacaine to reduce pain score in post-operative period. When adjuvants were added to ropivacaine in wound infiltartion, pain scores were decresed significantly. Shaman *et al.* also stated that ropivacaine plus dexmedetomidine in local wound infiltration had significantly low pain score compared to ropivacaine alone for cesarean section.[5] Demiraran *et al.* revealed in their study that wound infiltration with tramodol at cesarean section had lower VAS score compared to saline group.[48] Murat *et al.* also found that tramodol in wound infiltration had lower pain scores. These findings were in correlation with our study.[34]

Duration of analgesia as defined by time for first rescue analgesic was significantly shorter in control group compared to other groups. Time for first rescue analgesic was longest for ropivacaine-tramodol group among all three groups. Our study revealed that duration of post-operative analgesia was higher in ropivacaine-tramodol group compared to ropivacaine group and saline group. Ozyilmaz *et al.* revealed that in lumbar disk surgeries, time for first recsue analgesic was ealiest in saline group followed by levobupivacaine group and then tramodol group.[47] In contrast to our study, Anders *et al.* found that wound infiltration with ropivacaine with or without fentanyl had no effects on post-operative pain relief after breast surgery.[32] Mitra *et al.* demonstrated that wound infiltration with tramadol as adjuvant to ropivacaine for lumber discectomies had longer time for first rescue analgesic requirement. These findings were in accordance to our study.[39] So, local anesthetics in wound infiltration could prolong duration of post-operative analgesia. When adjuvants (tramodol in our study) were added to local anesthetics, duration of analgesia was significantly prolonged.

Number of rescue doses in first *24 hrs* was higher in saline group compared to other two groups. These findings were indicating that patients with wound infiltration with local anesthetics required less rescue analgesic and better pain control. Mohta *et al.* found that there was less requirement of rescue doses in local anesthetic infiltration compared to control group for tubercular spine surgery.[17] Lee *et al.* also revealed similar findings for single incision laproscopic colectomy.[10] In contrast to our study, Murat *et al.* revealed in their study of wound infiltration for cesarean delivery that there was no difference between saline group and tramadol group in terms of rescue dose requirement.[34]

Rescue dose requirement were also higher for ropivacaine group compared to ropivacaine-tramodol group. These was might be due to addition of opioids (tramodol in our study) to local anesthetic in wound infiltration could prolong duration of analgesia. Mitra *et al.* revealed that local wound infiltration with ropivacaine-tramadol had no difference in rescue dose requirement compared to ropivacaine group.[39] Khajavi *et al.* found that subcutaneous wound infiltration with tramodol after renal surgery had lower rescue analgesic requirement.[14]

In our study, incidences of PONV in first *24 hrs* were nearly similar in all three groups. There was no increase incidence of PONV in ropivacaine-tramodol group. Khajavi *et al.* revealed that

subcutaneous tramodol infiltration after renal surgery had no increase risk for PONV.[14] Kong *et al*. also revealed that ropivacaine wound infiltration reduced incidence of PONV.[50] These findings were in correlation with our study. There was no increased incidence of PONV in ropivacaine-tramodol group indicating better safety profile of tramodol.

In our study, highest patient satisfaction at *24 hrs* was seen with ropivacaine-tramodol group and lowest with control group. These might be due to better quality of pain control with prolonged analgesia in ropivacaine-tramodol group. These findings also suggested that wound infiltration could provided better post-operative analgesia as part of multimodal approach hence better patient satisfaction. Mohta *et al.* found that patient satisfaction was higher for wound infiltration with local anesthetics compared to control group for tubercular spine surgery.[17]

Limitations

Wound infiltration as a part of multimodal approach should be considered in term of opioid sparing analgesic method. There are certain limitations to our study. Firts of all, sample size selected in our study was small and results obtained could not be applied to general populations. Second, surgeries were done by different surgeons hence tissue handling and wound infiltration done by them might affect results of our study. Third, it would be better to take follow up for atleast *48 hrs* post-operatively for more accurate results. So, we could access post,operative pain in late post, operative period, duration of hospital stay and any complications if any.

Conclusion

Both, ropivacaine and ropivacaine plus tramodol, in wound infiltration were highly effective for post-operative analgesia in open cholycystectomy surgeries. Ropivacaine-tramodol combination might be preferred in wound infiltration because of prolong duration of analgesia, least rescue analgesic requirement and better patient satisfaction without increase incidences of PONV.

References

1. Wightman JA. A prospective survey of the incidences of post-operative pulmonary complications. Br J Surg. 1968;55:85–91.
2. Latimer RG, Dickman M, Day WC, *et al.* Ventilatory patterns and pulmonary complications after upper abdominal surgery determined by pre-operative and post-operative computerized spirometry and blood gas analysis. Am J Surg. 1971;122:622–32.
3. Sun JX, Bai KY, Liu YF, *et al.* Effects of local wound infiltration with ropivacaine on post-operative pain relief and stress response reduction after open hepatectomy. World J Gastroenterol. 2017;23(36):6733–740.
4. Zhu H, Wang C, Xu C, *et al.* Influence of patient-controlled epidural analgesia versus patient-controlled intravenous analgesia on post-operative pain control and recovery after gastrectomy for gastric cancer: A prospective randomized trial. Gastric Cancer. 2013;16:193–200.
5. Bhardwaj S, Devgan S, Sood D, *et al.* Comparison of local wound infiltration with ropivacaine alone or ropivacaine plus dexmedetomidine for post–operative pain relief after lower segment cesarean section. Anesth Essays Res. 2017;11(4):940–45.
6. Dahl JB, Jeppesen IS, Jorgensen H, *et al.* Intra-operative and post-operative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: A qualitative and quantitative systematic review of randomized controlled trial. Anesthesiology. 1999;91:1919–927.
7. Gehlin M, Tryba M. Risks and side effects of intrathecal morphine combined with spinal anesthesia: A meta-analysis. Anesthesia. 2009;64:643–51.
8. Wu CL, Cohen SR, Richman JM, *et al.* Efficacy of post-operative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: A meta-analysis.Anesthesiology. 2005;103:1079–088.
9. Scott NB. Wound infiltration for surgery. Anesthesia. 2010.65S:67–75.
10. Lee KC, Lu CC, Lin SE *et al.* Infiltration of local anesthesia at wound site after single-incision laproscopic colectomy reduces post-operative pain and analgesic usage. Hepato Gastroenterology. 2015;62:811–16.
11. Moiniche S, Mikkelsen S, Wetterslev J, *et al.* A systematic review of incisional local anesthesia for post-operative pain after abdominal operations. Brit Anesth. 1998;81:377–83.
12. Vigneau A, Salengro A, Berger J, *et al.* A double blind randomized trial of wound infiltration with ropivacaine after breast cancer surgery with axillary nodes dissection. BMC Anesthesiol. 2001;24:11–23.
13. Udita Naithani, Indira Kumari, Rekha Roat, *et al.* Efficacy of wound infiltration using bupivacaine versus ropivacaine along with fentanyl for post-operative analgesia following abdominal

hysterectomy under spinal anesthesia. Journal of Evolution of Medical and Dental Sciences. 2013;2(34):6478–489.

14. Kuthiala G, Chaudhary G. Ropivacaine: A review of its pharmacology and clinical use. Indian J Anesth. 2011;55:104–110.
15. Leone S, Di Cianni S, Csati A, *et al.* Pharmacology, toxicology and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. Acta Biomed. 008;79:92–105.
16. Swain A, Nag DS, Sahu S, *et al.* Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases. 2017;5:307–323.
17. Mohta M, Rani A, Sethi AK, *et al.* Efficacy of local wound infiltration analgesia with ropivacaine and dexmedetomidine in tubercular spine surgery: A pilot randomized double-blind controlled trial. Indian J Anesth. 2019;63:182–87.
18. Khajavi MR, Navardi M, Shariat Moharari R, *et al.* Combined ketamine-tramadol subcutaneous wound infiltration for multimodal post-operative analgesia: A double blind randomized controlled trial after renal surgery. Anesth Pain Med. 2016;6(5):e37778.
19. Sachidananda R, Joshi V, Shaikh SI, *et al.* Comparison of analgesic efficacy of wound infiltration with bupivacaine versus mixture of bupivacaine and tramadol for post-operative pain relief in cesarean section under spinal anesthesia: A double blind randomized trial. J Obstet Anesth Crit Care. 2017;7:85–89.
20. Merskey H, Bogduk N. Classification of chronic pain second edition. Seatttle: IASP Task Force on Taxonomy, IASP Press; 1994.
21. Hosseini Jahromi SA, Sadeghi Poor S, Hosseini Valami SM, *et al.* Effects of suppository acetaminophen, bupivacaine wound infiltration and caudal block with bupivacaine on post-operative pain in pediatric inguinal herniorrhaphy. Anesth Pain. 2012;1(4):243–47.
22. Gousheh SM, Nesioonpour S, Javaher Foroosh F, *et al.* Intravenous paracetamol for post-operative analgesia in laproscopic cholecystectomy. Anesth Pain Med. 2013;3(1):214–18.
23. Wils VL, Hunt DR. Pain after laproscopic cholecystectomy. Br J Surg. 2000;87:273.
24. Ahmad khan, Shabir Ahmad Sofi, Farhana Bashir, *et al.* A comparative study showing efficacy of preemptive intravenous paracetamol in reducing post-operative pain and analgesic requirement in laproscopic cholecystectomy. J of Evol of Med and Dent Sci. 2015;4(62):10771–77.
25. Imani F, Rahimzadeh P, Faiz SHR. Comparison of the efficacy of adding clonidine, chlorpromazine, promethazine and midazolam to morphine pumps in post-operative pain control of addicted patients. Anesth Pain. 2011;1(1):10–14.
26. Shoar S, Esmaeili S, Safari S. Pain management after surgery: A brief review. Anesth Pain 2012;1(3):184–86.
27. Lee RM, Tey JBL, Chua NHL. Post-operative pain control for total knee arthroplasty: Continuous femoral nerve block versus intravenous patient controlled analgesia. Anesth Pain. 2012;2(3):184–86.
28. Sujata N, Hanjoora VM. Pain control after cesarean birth-what are the options? J Gen Pract. 2014;2:164.
29. Ashburn MA, Caplan RA, Carr DB. Practice guidelines for acute pain management in the peri-operative setting. An updated report by the American Society of Anesthesiologists task force on acute pain management. Anesthesiology. 2004;100:1573–81.
30. Rawal N, Axelsson K, Hylander J, *et al.* Post-operative patient-controlled local anesthetic administration at home. Anesth Analg. 1998;86:86–89.
31. Marques EM, Jones HE, Elvers KT, *et al.* Local anesthetic infiltration for peri-operative pain control in total hip and knee replacement: Systematic review and meta-analyses of short and long-term effectiveness. BMC Musculoskelet Disord. 2014;15:220.
32. Anderson L, Kehlet H. Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: A systemic review. Br J Anesth. 2014;113:360–74.
33. Gottschalk A, Burmeister MA, Radtke P, *et al.* Continuous wound infiltration with ropivacaine reduces pain and analgesic requirement after shoulder surgery. Anesth Analg. 2003;97:1086–91.
34. Haliloglu M, Bilgen S, Menda F, *et al.* Analgesic efficacy of wound infiltration with tramadol after cesarean delivery under general anesthesia: Randomized trial. J Obstet Gynecol Res. 2016;42(7):816–21.
35. Singh S, Prasad C. Post-operative analgesic effect of dexmedetomidine administration in wound infiltration for abdominal hysterectomy: A randomized control study. Indian J Anesth. 2017;61:494–98.
36. Brennan TJ, Zahn PK, Pogatzki-Zahn EM. Mechanisms of incisional pain. Anesthesiol Clin North America. 2005;23:1–20.
37. Kawamata M, Takahashi T, Kozuka Y, *et al.* Experimental incision-induced pain in human skin: Effects of systemic lidocaine on flare formation and hyperalgesia. Pain. 2002;100:77–89.
38. Whiteside JB, Wildsmith JA. Developments in local anesthetics drugs. Br J Anesth. 2001;87:27–35.
39. Mitra S, Purohit S, Sharma M. Post-operative analgesia after wound infiltration with tramadol and dexmedetomidine as an adjuvant

to ropivacaine for lumbar discectomies:A randomized-controlled clinical trial. J Neurosurg Anesthesiol. 2017;29(4):433–38.

40. Mehta TR, Parikh BK, Bhosale GP, *et al.* Post-operative analgesia after incisional infiltration of bupivacaine *vs* bupivacaine with buprenorphine. J Anesthesiol Clin Pharmacol. 2011;27(2):211–14.
41. Tverskoy M, Braslasky A, Mazor A, *et al.* The peripheral effect of fentanyl on post-operative pain. Anesth Analg. 1998;87:1121–124.
42. Mostafa GM, Mohamad MF, Bakry RM, *et al.* Effect of tramadol and ropivacaine infiltration on plasma catecholamine and post-operative pain. J of American Sci. 2011;7(7):473–79.
43. Vikers MD, O'Flaherty D, Szekely SM, *et al.* Tramadol pain relief by an opioid without depression of respiration. Anesthesia. 1992;47:291–96.
44. Sacerdote P, Bianchi M, Manfredi B, *et al.* Effects of tramadol on immune responses and nociceptive thresholds in mice. Pain. 1997;72:325–30.
45. Acalovschi I, Cristea T, Margarit S, *et al.*Tramadol added to lidocaine for intravenous regional anesthesia. Anesth Analg. 2001;92:209–14.
46. Gissen AJ, Gugino LD, Datta S, *et al.* Effects of fentanyl and sufentanyl on peripheral mammalian nerves.Anesth Analg. 1987;66:1272–76.
47. Ozyilmaz K, Ayoglu H, Okyay RD, *et al.* Post-operative analgesic effects of wound infiltration with tramadol and levobupivacaine in lumbar disk surgeries. J Neurosurg Anesthesiol. 2012;24(4):331–35.
48. Demiraran Y, Albayrak M, Yorulmaz IS, *et al.* Tramadol and levobupivacaine wound infiltration at cesarean delivery for post-operative analgesia. J Anesth. 2013;27(2):175–79.
49. Baudry G, Steghens A, Laplaza D, *et al.* Ropivacaine infiltration during breast cancer surgery. Ann Fr Anesth Reanim. 2008;27:979–86.
50. Kong TW, Park H, Cheong JY, *et al.* Efficacy of continuous wound infiltration of local anesthetic for pain relief after gynecologic laproscopy. Int J Gynaecol Obstet. 2014;124:212–15.