Research Paper Volume - 3 | Issue - 5 | September - 2019 | ISSN (O) : 2663-0729 | ISSN (P) : 2663-0710

A COMPARATIVE STUDY BETWEEN INTRAVENOUS FENTANYL AND INTRAVENOUS KETOROLAC AS INTRAOPERATIVE ANALGESIC AGENTS FOR PATIENTS UNDERGOING SURGERY UNDER GENERAL ANAESTHESIA.

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ABSTRACT

Introduction: Adequate control of perioperative pain is important for both short and long-term patient outcome. Perioperative pain leads to neural sensitization resulting in persistent postoperative pain1.

Aim-This study was conducted to compare IV fentanyl and IV ketorolac as intra operative analgesic agents for patients undergoing elective surgery under general anaesthesia.

Setting and Design- Academic institute. Prospective randomized study.

Methods: The study was performed over two years with the age group 18 to 80 years of both sexes and of ASA physical status Grade I, II or III allocated to 2 groups, Group F-fentanyl and Group K-ketrolac at premedication. Patients were monitored for HR, BP and other effects during perioperative period.

Statistical Methods Applied: Descriptive and inferential statistical analysis was applied in this study. Student't' test was used on continuous scale between two groups (F & K) and Chi- square test on categorical data. Significance is assessed at 5 % level.

Results: In the groups studied, the mean age, sex, weight, duration of surgery was comparable. The mean basal HR was comparable in both groups. The mean HR, blood pressure was significantly higher in Group-K during intra- and postoperative period. Patients in Group-F were more sedated, postoperatively. Patients in Group-K had lesser side effects.

Conclusion: Study concludes that use of ketorolac provides acceptable analgesia but found superior pain relief in the group treated with fentanyl. A decided advantage of ketorolac over fentanyl is the absence of nausea, vomiting, pruritus and urinary retention and less sedation in the postoperative period.

KEYWORD

Fentanyl , Ketorolac, Perioperative pain, VAS, Adverse effects .

ARTICLE HISTORY

Submitted: 09-04-2019 **Accepted: 04-07-2019** **Published: 10-09-2019**

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INTRODUCTION

Adequate control of perioperative pain (intraoperative pain relief) is important for short-term and long-term patient outcome as perioperative pain may lead to neural sensitization potentially resulting in persistent postoperative pain[1] and related complications. This pain relief may require the use of narcotic and non-narcotic medications, anti-anxiety medications, and other techniques. Narcotic analgesics, fentanyl has long been, and continues to be, part of the anaesthesiologist's armamentarium for the treatment of perioperative pain, often underutilized because of its inherent drug related adverse effects. Among the non-narcotic analgesics, ketorolac, a non-selective NSAID- with potent analgesic efficacy is used intraoperatively to avoid opiods side-effects.

AIMS AND OBJECTIVES

This study was conducted to compare IV fentanyl and IV ketorolac as intra operative analgesic agents for patients undergoing surgery under general anaesthesia. To assess their capability as analgesic agents, their effects on hemodynamic parameters and their side effects.

METHODS AND MATERIALS

This is a prospective randomized study of 100 patients undergoing elective surgical procedure under general anesthesia in People's Education Society Institute of Medical Sciences & Research Kuppam - 517425, Chittoor Dist., Andhra Pradesh. The study period was for two years, from September 2014 to September 2016. Patients belonging to age group 18 to 80 years of both sexes and of ASA physical status Grade I, II or III randomly allocated to 2 groups, each having 50 patients Group F and Group K. Group F patients received 2µg/Kg fentanyl and the Group K patients received 0.5mg/kg of ketorolac intravenously at the time of pre medication along with 0.2 mg of glycopyrrolate. The following exclusion criteria was used- ASA physical status grade IV or V, age less than 18 years, pregnant patients, history of peptic ulcer, history of coagulopathies, history of allergy or intolerance to NSAIDs, alcohol or opioid abuse, patients with clinically significant cardiovascular, respiratory, hepatic, renal, neurological, psychiatric, metabolic disease, patients not willing for the study.

A standard induction consisting of propofol, vecuronium and

inahalation anaesthetic of isofurane and nitrous-oxide & oxygen was used. Inspired volatile anesthetic concentration was adjusted as necessary to maintain pulse and NIBP within 20% of pre-induction values. Supplemental doses of analgesic drug were used to control acute changes or if there were other signs of inadequate analgesia. Neostigmine with glycopyrrolate was given, to antagonize the residual neuromuscular block at the end of surgery and extubated as per the standard protocol. None of the patients received blood transfusion, sympathomimetic drugs or analgesics other than the study medications. Urine output was monitored wherever necessary.

Post operatively patient was closely monitored for hemodynamic effects and respiratory depression. The time for the first rescue analgesic medication and number of times it is required in the next 24 hours was noted. Patient was observed for side effects like hypotension, respiratory depression, sedation, urticarial, oozing of blood from surgical site and urinary retention.

METHODS OF COLLECTION OF DATA

The following parameters were compared in the groups- Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Peripheral oxygen saturation. These parameters were recorded before and at 5minute interval from the time of premedication upto 25th minute. Sedation scoring was scored by using- Ramsay sedation scale. Post-operative pain accessed on Visual Analog Scale (VAS). Patients were oriented to VAS score.

STATISTICAL METHODS APPLIED

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Suggestive significance – p-value: $0.05<p<0.10$ Moderately significant - p-value: $0.01<p\leq 0.05$ Strongly significant - p-value: $p\leq 0.01$.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square test has been used to find the significance of study parameters on categorical scale between two or more groups. Statistical software namely SPSS 15.0, Stata 13, MedCalc 9.0.1 and Systat 12.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables.

RESULTS

AGE DISTRIBUTION

The mean age in group F was 36.54±13.41 and group K was 34.50±11.78. There was no difference in the mean age between the groups. The largest group of patients was in second decade of life.

AGE IN YEARS	Group F		Group K	
	No. of patients	Percentage	No. of patients	Percentage
18-30	23	46.0	26	52.0
31-40	8	16.0	10	20.0
41-50	12	24.0	10	20.0
51-60	5	10.0	24	61.0
61 &Above	2	4.0	2	4.0
TOTAL	50	100	50	100
Mean age in years ±SD	36.54 ± 13.41		34.50± 11.78	
p-value	0.4836(NS)			

Figure-1 showing the age distribution

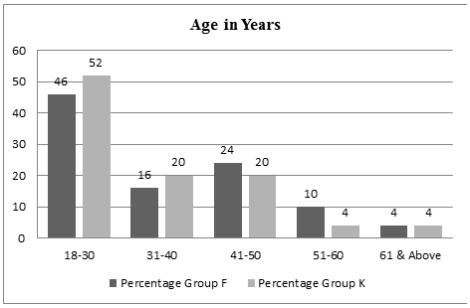
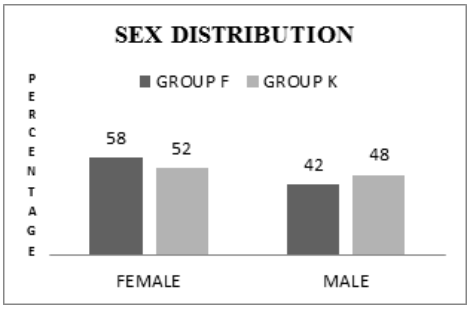


TABLE-2 DEPICTING SEX DISTRIBUTION:

	Group F	Group K	p-value
FEMALE	29(58%)	26(52%)	0.456(NS)
MALE	21(42%)	24(48%)	

Demographical analysis showed a distribution of 58% females and 42% males in Group F, 52% female and 48% male in group K. There was no significant difference.

Figure-2. Showing the sex distribution



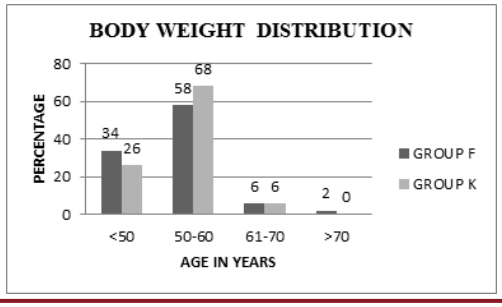
BODYWEIGHT DISTRIBUTION

Table-3 Showing the body weight distribution

Body weight (kg)	Group F		Group K	
	No of Patients	Percentage	No of Patients	Percentage
<50	17	34.00	13	26.00
51-60	29	58.00	34	68.00
61-70	3	6.00	3	6.00
>70	1	2.00	0	0.00
Total	50	100	50	100
Mean body weight in kg ± SD	55.54 ± 6.33		55.08 ± 6.13	
Minimum body weight in kg	40		32	
Maximum body weight in kg	78		69	
p-value	0.9021(NS)			

The maximum body weight recorded was 78 kgs and 69 kgs respectively. The mean body weight in Group F was 55.54±6.33and in Group K it was 55.08±6.13. There was no significant difference in the body weight of patients between the Group F and Group K. (p= 0.9021).

Figure-3 Showing the body weight distribution



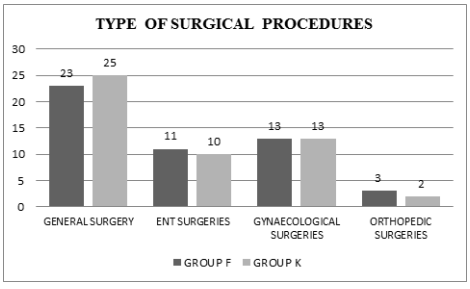
TYPE OF SURGICAL PROCEDURE

Table 4. Showing the type of surgical procedures in Group-F and Group-K

Type of surgical procedure	Group F	Group K
General surgeries	23(46%)	25(50%)
ENT surgeries	11 (22%)	10 (20%)
Gynaecological surgeries	13 (26%)	13 (26%)
Orthopaedic surgeries	3 (6%)	2(4%)
p-value	0.954(NS)	

Table shows the type of surgery patients have undergone in both groups.There was no significant difference in the type of surgical procedure between the two groups. (p= 0.954).

Figure 4. Showing the type and number of surgical procedures



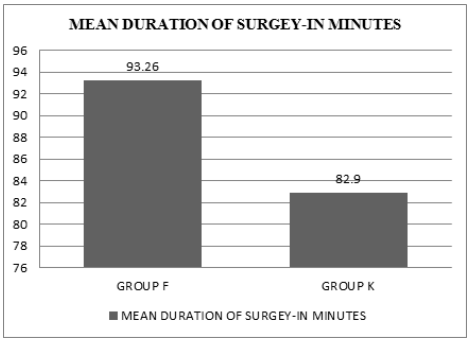
DURATION OF SURGERY:

Table 5. Showing mean duration of surgery between Group-F and Group-K

	Mean duration of surgery (In minutes)
Group F	93.26 ± 30.85
Group K	82.90 ± 31.19
p-value	0.0981(NS)

The total duration of surgery was counted in Minutes for both groups, the mean duration of surgery in Group F is 98.26 minutes, and the mean duration of surgery in Group K is 82.90 minutes. In both the study and control group the duration of surgery was found comparable with the p value being > 0.05 which is not significant.

Figure 5. Showing the mean duration of surgery



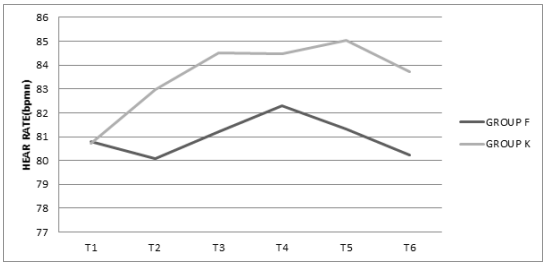
MEAN HEART RATE CHANGES

Table 6. Showing the intergroup comparison of intra operative mean heart rate (bpm) changes in Group-F and Group-K

Time	Group F	Group K	p-value
T1	80.78 ± 5.49	80.72 ± 5.45	0.9564 (NS)
T2	80.08 ± 5.42	82.98 ± 6.55	0.0344 (S)
T3	81.22 ± 6.07	84.52 ± 6.44	0.0097 (HS)
T4	82.28 ± 7.17	84.46 ± 7.31	0.1354 (NS)
T5	81.32 ± 7.30	85.04 ± 7.37	0.0128 (S)
T6	80.24 ± 6.08	83.72 ± 8.23	0.0181 (S)

The mean basal HR were comparable in both groups (p=0.9564). The mean HR observed at T2, T3, T4, T5, T6 intervals were higher in group K when compared to group F.

Figure 6. Showing the intergroup comparison of intra operative mean heart rate (bpm) changes in Group-F and Group-K



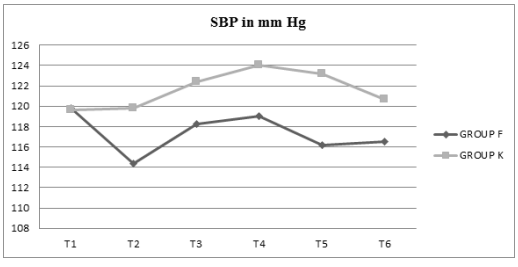
MEAN SBP CHANGES

Table 7. Showing the intergroup comparison of intra operative mean systolic blood pressure changes (SBP in mm Hg) in Group-F and Group-K

Time Group	Group F	Group K	p-value
T1	119.84 ± 11.95	119.60 ± 11.84	0.9199 (NS)
T2	114.40 ± 11.25	119.82 ± 09.93	0.0122 (S)
dT3	118.24 ± 13.45	122.40 ± 10.32	0.0858 (NS)
T4	119.02 ± 11.93	124.06 ± 09.96	0.0239 (S)
T5	116.16 ± 11.12	123.14 ± 14.50	0.0077 (HS)
T6	116.48 ± 10.80	120.70 ± 11.23	0.0584 (NS)

There was a significant increase in SBP in Group-K as compared to Group-F.

Figure 7. Showing the intergroup comparison of intra operative mean systolic blood pressure changes (SBP in mm Hg) changes in Group-F and Group-K



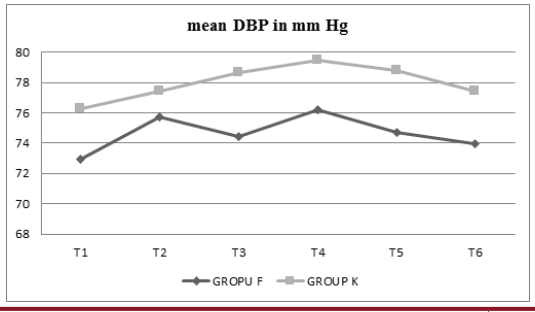
MEAN DBP CHANGES

Table 8. Showing the intergroup comparison of intra operative mean diastolic blood pressure (DBP in mmHg) changes in Group-F and Group-K

Time	Group F	Group K	p-value
T1	72.94 ± 8.17	76.24 ± 5.71	0.1082 (NS)
T2	75.70 ± 7.46	77.40 ± 6.82	0.3767 (NS)
T3	74.44 ± 8.57	78.66 ± 6.43	0.0064 (HS)
T4	76.20 ± 7.31	79.44 ± 8.13	0.0300 (S)
T5	74.74 ± 7.34	78.80 ± 9.83	0.0400 (S)
T6	73.64 ± 7.24	77.44 ± 6.69	0.0076 (HS)

Similar to SBP, there was a relatively a higher DBP in Group-k.

Figure 8. Showing the intergroup comparison of intra operative mean diastolic blood pressure (DBP in mmHg) changes in Group-F and Group-K



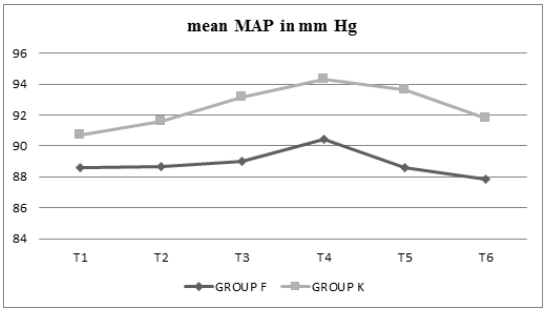
MEAN MAP CHANGES

Table 9. Showing the intergroup comparison of intra operative mean arterial pressure (MAP in mmHg) changes in group F and group K

Time	Group F	Group K	p-value
T1	88.60 ± 8.51	90.68 ± 6.23	0.4498 (NS)
T2	88.64 ± 7.70	91.60 ± 7.02	0.1226 (NS)
T3	89.04 ± 9.19	93.14 ± 6.77	0.0127 (HS)
T4	90.42 ± 8.13	94.30 ± 6.55	0.0100 (S)
T5	88.58 ± 7.94	93.64 ± 10.04	0.0116 (S)
T6	87.88 ± 7.61	91.82 ± 5.99	0.0050 (HS)

There was a significant increase in MAP in those patients treated with Ketrolac.

Figure 9. Showing the intergroup comparison of intra operative mean arterial pressure (MAP in mmHg) changes in group F and group K



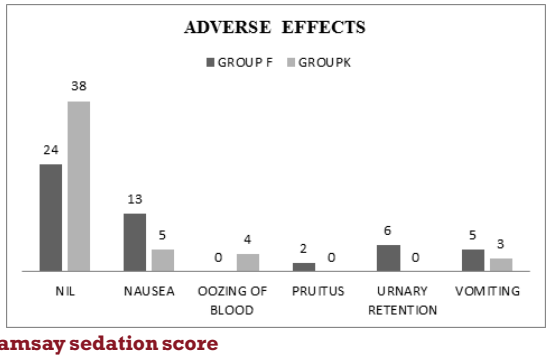
ADVERSE EFFECTS

Table 10. Showing the adverse effects between group F and group K

	Nil	Nausea	Oozing of blood from surgical site	Pruritus	Urinary retention	Vomiting
Group F	24	13	0	2	6	5
Group K	38	5	4	0	0	3
p-value	0.002(HS)					

In Group F, none of the patients had oozing of blood from surgical site. In Group K none of the patients had side effects like pruritus and urinary retention.

Figure 10. Showing the side effects between group F and group K



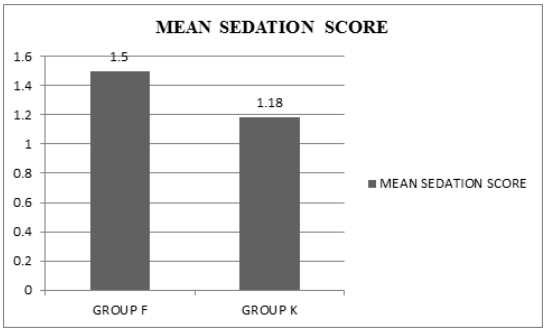
Ramsay sedation score

Table 11. Showing the sedation score between group F and group K

	Mean sedation score
Group F	1.50 ± 0.51
Group K	1.18 ± 0.39
p-value	0.0008 (HS)

In group F sedation score was 1.50±0.51 and in group K the score was 1.18±0.39. Statistical evaluation showed highly significant difference in the sedation score between the two groups ($p<0.01$).

Figure 11. Showing the sedation score between group F and group K



Discussion

The International Association for the Study of Pain describes pain as an unpleasant subjective experience with sensory and emotional features arising from actual or potential tissue damage[2].

Adequate control of acute pain is important for both short-term and long-term patient outcomes as perioperative pain may lead to neural sensitization potentially resulting in persistent postoperative pain[1].

Types of pain relief in the perioperative period include opioid and non-opioid analgesic medications. Opioid analgesics have long been, and continue to be, part of the anaesthesiologist's armamentarium for the treatment of perioperative pain. However, opioids are often under-dosed due to concerns about side effects including respiratory depression, urinary retention, gastrointestinal upset, Central nervous system (CNS) depression and dermatologic effects.

A systematic review of the literature from 1990 to 2000 characterized opioid associated adverse events in post-operative patients. The most severe of these adverse effects is respiratory depression[3]; gastrointestinal effects were second most frequently reported side effects, urinary retention more so in spinal opioids and pruritus in epidural opioids. Nevertheless, most of the adverse drug effects of opioids are dose related and the authors conclude that opioid limiting strategies are desirable[3].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are widely prescribed on out patient management but are often held in the perioperative period due to concern for increased intraoperative bleeding[4,5]. Ketorolac is a non-selective NSAID with potent analgesic effects that can be given intravenously, intramuscularly, orally and topically without respiratory or central nervous system depression effects[6]. A meta-analysis of thirteen randomized trials demonstrated that single dose systemic ketorolac decreased early post-operative pain and had opioid sparing effects. Additionally, the use of ketorolac as part of a multimodal pain strategy reduced post-operative nausea and vomiting[6]. Alexander et al[7] demonstrated that a single dose of pre-operative diclofenac or ketorolac reduced morphine consumption by 29% compared to placebo with an additional decrease in post operative nausea, vomiting and pruritus in patients undergoing Total Joint Arthroplasty (TJA)[7]. Moller PL et al[8] and Memis D et all[9] used paracetamol against opioids and documented reduced opioid related adverse events.

In our present study, there was no stastically significant difference in demographical variables. The duration of surgery and type of surgery was matched in between the groups.

We found a high HR and a significant increase in blood pressure in Group-K as compared to Group-F. Studies by Manuel Ramirez et al[10], Amr M. Yassen et al[11] showed no significant difference between the groups studied. Our study found a relatively higher incidence of HR and blood pressure

probably because our case series are not out-patient based type of surgeries.

In group F mean sedation score immediately after extubation was 1.50 ± 0.51 and 1.18 ± 0.39 in group K which is statistically highly significant (p=0.0008). Amr M. Yassen et al[11] Campbell et al[12] also had a similar findings.

The mean V.A.S score in group F was 4.14 ± 0.35 and in group K was 4.76 ± 0.66-indicating high post-op pain in Group-K. Similar to our study, there was a significant increase in pain in studies done by Jin Hyung Kim et al[13] study in eviscerated patients, Yifeng Ding[14], Cepeda M. Soledad et al[15] also noted mean pain scores were less in morphine group than in ketorolac group.

With respect to adverse effects, no adverse effects were observed in 38 patients in group K when compared to 24 patients in group F. The incidence of nausea and vomiting in the present study was significantly lower in the group K compared to the group F. These results were in agreement with previous work by Manuel Ramirez et al[10], Radha et al[16] and by Parker et al[17]. Thagaard et al[18] reported an anti-emetic effect of ketorolac in different post-operative settings. Jin Hyung Kim et al[13] found similar incidence but was not significant.

Four patients in group K developed oozing at surgical site on the day of surgery, none in group F. In the study conducted by Philip Balestrieri et al[19], three patients in the ketorolac postoperative group had significant bleeding, requiring transfusion of blood; however, these events were rated as "probably not" related to the study medication.

Two patients in group F developed pruritus and urinary retention as compared to none in group k. Data from Voytek Bosek et al[20] study confirm that intraoperative administration of opioids is associated with a significant frequency of pruritus.

CONCLUSION

The present study concludes that the use ketorolac provides acceptable analgesia but found superior pain relief in the group treated with fentanyl, ketorolac has no apparent advantage over fentanyl. . . [but] may have a place in the treatment of pain in patients in which the sedative effects of the opioids would be disadvantageous". A decided advantage of ketorolac over fentanyl is the absence of nausea, vomiting, pruritus and urinary retention and less sedation in the postoperative period.

REFERENCES

1) Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. Yale J Biol Med 2010;83:11-25.
2) Merskey H, Bogduk N (eds): Classification of Chronic Pain (ed 2). Seattle, WA, IAPS task force on taxonomy, IAPS Press, 1994.
3) Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain. 2002; 3: 159180.
4) Moiniche S, Romsing J, Dahl JB, Tramèr MR. Nonsteroidal anti-inflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. Anesth & Analg. 2003; 96: 68-77.
5) Strom BL, Berlin JA, Kinman JL, Spitz PW, Hennessy S, Feldman H, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A post marketing surveillance study. JAMA. 1996; 275: 376- 382.
6) De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. Anesth & Analg. 2012; 114: 424-433.
7) Alexander R, El-Moalem HE, Gan TJ. Comparison of the morphine-sparing effect of diclofenac sodium and ketrolac tromethamine after major orthopaedic surgery. J. Clin. Anesth. Vol-14, Issue-3, 187-192.
8) Moller PL, Julh GI, Payen-Champenois C, Skoglund LA. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. Anesth & Analg. 2005; 101: 90-96.
9) Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the suse of opioids, extubation time and opioid-related adverse effects after major surgery in intensive care unit. J Crit Care. 2010; 25: 458-62.
10) Manuel Ramirez-Ruiz, MD, Ian Smith, BS, MB, FRCA, Paul F. White, PhD, MD, FANZCA. Use of analgesics during propofol: A comparison of ketorolac, dezocine, and fentanyl. J. Clin. Anesth. Vol-7, Issue-6: 481-485, 1995.
11) Amr M. Yassena, Gamal El Sayed. Low dose ketorolac infusion improves postoperative analgesia combined with patient controlled fentanyl analgesia after living donor hepatectomy- Randomized controlled trial. Egyptian Journal of Anaesthesia (2012) 28, 199–204.
12) Campbell SC, Krumpe P, Shepard J. Ventilatory effects of ketorolac and morphine in chronic obstructive pulmonary disease. Drug Invest 1993; 5 (I): 1-10.
13) Jin Hyung Kim, Sun Young Jang, Myung Jin Kim, Sang Yeul Lee, Jin Sook Yoon. Comparison of Pain-relieving Effects of Fentanyl versus Ketorolac after Eye Amputaion Surgery. Korean J Ophthalmol Vol. 27, No. 4, 2013-Pg-229.
14) Ding, Yifeng ; Fredman, Brian; White, Paul F. Use of ketorolac and fentanyl during Outpatient Gynecologic Surgery. Anesth & Analg 1993; 77: 205-210.
15) Cepeda, M. Soledad; Vargas, Liliana; Ortegon, Gloria et al. Comparative Analgesic Efficacy of Patient-Controlled Analgesia with Ketorolac Versus Morphine After Elective Intra abdominal Operations. Anesth & Analg 1995; Vol-80: Isuue 6-p 1150-1153.
16) Sukhani, Radha MD; Vazquez, John MD; Pappas, Ana L. MD et al. Recovery After Propofol With and Without Intraoperative Fentanyl in Patients Undergoing Ambulatory Gynecologic Laparoscopy. Anesth & Analg 1996; Vol-83: Issue-5- p975-981.
17) Parker RK, Holtmann B, Smith I, White PF. Use of ketorolac after lower abdominal surgery. Effect on analgesic requirement and surgical outcome. Anaesthesiology 1994; 80(1): 6–12.
18) Thagaard KS, Jensen HH, Raeder J. Analgesic and antiemetic effect of ketorolac vs. betamethasone or dexamethasone after ambulatory surgery. Acta Anaesthesiology Scand 2007; 51(3): p 271–277.
19) Philip Balestrieri MD, Gary Simmons MD, Douglas Hill et al. The effect of intravenous ketorolac given intraoperatively versus postoperatively on outcome from gynaecologic abdominal surgery. J. Clin. Anesth. Vol-9: p 358-364, 1997.
20) Voytek Bosek MD, Daniel B. Smith MD, Charles Cox MD. Ketorolac or fentanyl to supplement local anesthesia? J. Clin. Anesth. Vol-4: p 480-483, 1992.