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Research Article

A Comparative Study of Ketorolac, Paracetamol and Tramadol for Post-Operative Pain Management in General And Orthopedic Surgeries

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ABSTRACT

Pain or Algesia is an unpleasant bodily sensation usually evoked by an external or internal noxious stimulus. The amount of pain a patient goes through after a surgery is related to the site of surgery and extent of tissue damage. Less than half of the patients who have undergone surgery report of the adequate postoperative pain relief. Proper Post-operative pain control leads to reduction in length of hospital stay, aids in earlier patient mobilization and increased ability to perform daily living activities. The purpose of this study is to compare ketorolac, paracetamol and tramadol in terms of efficacy, safety and post-operative analgesia in patients undergoing orthopaedic and general surgeries. This is a prospective, randomized, comparative, observational study carried out on 120 patients of age 12-75 years undergoing orthopaedic and general surgeries. The patients were divided into three groups in which group 1 was given 30mg ketorolac intramuscularly, group 2 was given 1g paracetamol intravenously and group 3 was given 100mg tramadol intravenously. Duration of post-operative analgesia, pain score, pain onset time, median time to rescue analgesic, pain free interval, hemodynamic parameters and incidence of adverse effects were recorded and statistically analysed using chi-square test. The study concluded that, Ketorolac when given post-operatively is a more effective analgesic when compared with paracetamol and tramadol as it gives a longer duration of analgesia which decreases the use of rescue analgesic.

INTRODUCTION

As defined by the International Association for the study of Pain (IASP), pain is "an unpleasant sensory and emotional experience which is associated with actual or potential tissue injury or

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described in terms of such damage". [1] Pain act as warning against damage to the body which is very important to avoid injuries and consequently for survival of life. [2] Post-Operative Pain is defined as "a condition of tissue damage together with muscle spasm after surgery". The amount of pain a patient goes through after a surgery is related to the site of surgery and extent of tissue damage. Joint replacement surgeries cause severe postoperative pain. [3] Approximately 75% of patients who undergo surgery experience acute postoperative pain, which is usually medium-high in its severity. Less than half of the patients who have undergone surgery report of the adequate postoperative pain relief. [4] Proper Post-operative pain control leads to reduction in length of hospital stay, aids in earlier patient mobilization and ability to perform daily living activities and increases patient satisfaction. [4] Inappropriate pain management increases adverse physiological effects in the acute postoperative setting, chances of developing a chronic pain syndrome, complications and prolonged rehabilitation, reduction in quality of life and interfere with sleep and physical activity. [4] The objective of this study is to compare the effects of post-operative analgesia of ketorolac, paracetamol and tramadol through assessment of pain score, median time to rescue analgesics, pain free interval after first dose of analgesic, measurement of hemodynamic parameters before and after administration of analgesic, and assessment of adverse drug reactions associated with the drugs.

Physiology of Nociceptive Pain

It involves various stages such as stimulation, transmission, perception, modulation and adaptive inflammation. Stimulation of free nerve endings known as the nociceptors, distinguish between noxious and innocuous stimuli, and are activated and sensitized under mechanical, thermal, and chemical impulses. These stimuli cause the release of bradykinins, potassium ion (K+), prostaglandins, histamine, leukotrienes, serotonin, and substance P that sensitize and/or activate the nociceptors leading to action potentials that are transmitted along afferent nerve fibers to the spinal cord. [5] Transmission takes place through two fibres, A-delta fibres and C-afferent nerve fibers. These fibers synapse in various layers of the dorsal horn in the spinal cord, releasing a variety of neurotransmitters, which include glutamate, substance P, and calcitonin gene–related peptide. The interactions between neuroreceptors and neurotransmitters that take place in this synapse lead to the complex series of events that influence pain. With the thalamus acting as a relay station, these pain processes reach the brain through the spino-thalamic tract where pain can be processed further. [5] During pain perception, pain becomes a conscious experience that takes place in higher cortical structures. The brain accommodates only a limited number of pain signals. Various cognitive and behavioral functions modify pain. [5] Pain modulation occurs through a number of complex processes, one of them being the Endogenous opiate system which consists of neurotransmitters like enkephalins, dynorphins, and β-endorphins and receptors such as mu, delta and kappa that are found throughout the CNS. These endogenous opioids bind to opioid receptors and cause modulation of the transmission of pain impulses. [5] Inflammatory pain is the body's shifting from preventing tissue damage to the promotion of healing. As a result, the pain threshold is reduced and the injured area becomes more sensitive to pain. Due to this process, our contact with and movement of the injured area is decreased, thus promoting the progression of healing. In response to tissue damage and inflammation, there is a significant change in the chemical composition of the neurons that innervate the affected tissues reflecting various proteins expressed by the sensory neurons. Altered production of these proteins lead to modification

of the phenotype of the neurons, changing their transduction and transmission properties. [5]

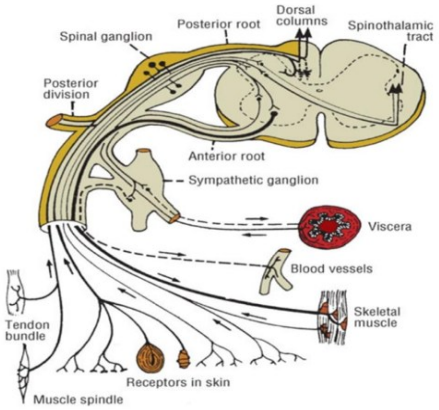


Fig 1: Schematic Representation of Nociceptive Pain. [5]

Acute Pain Relief Treatment Chart

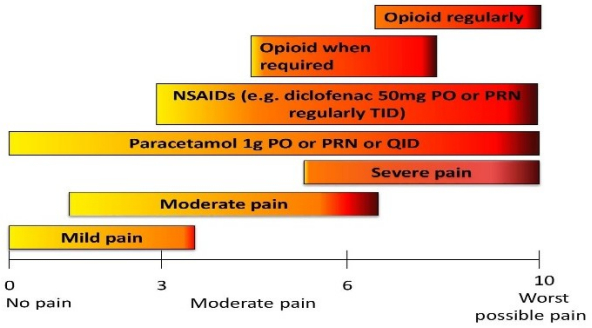


Fig 2: Acute Pain Relief Treatment Chart. [6]

Mild pain – paracetamol; Mild-moderate pain – paracetamol, NSAIDS; Moderate-severe pain – opioid when required; Severe pain – opioid regularly. [6]

The Oxford League Table

The Oxford League Table was designed by the Oxford pain group for acute pain wherein each analgesic is given a specific number to grade its efficacy. [7] Analgesic efficacy is expressed as the number-needed-to-treat (NNT) i.e. the number of patients who are needed to receive the active drug in order to achieve at least 50% pain relief compared with placebo over a 4- 6 hour treatment period. [8] Recent evidence proves that the efficacy of each analgesic is different and hence, the oxford league table is a good tool to determine the relative efficacy of analgesics. [7] The most effective analgesic has a low NNT value of approximately 2. It means, for every two patients who had received the drug, one patient will get a minimum of 50% relief due to the drug (the other patient may or may not have relief but it does not reach the 50% level). [7]

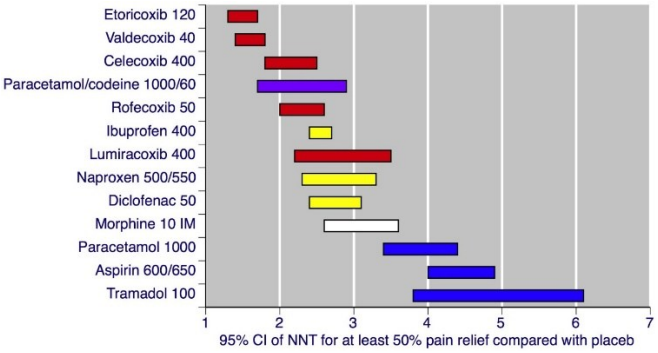


Fig 3: League Table Of Numbers Needed To Treat (NNT) For At Least 50% Pain Relief Over 4-6 Hours In Patients With Moderate To Severe Pain. [7]

Oxford League Table of Analgesia

Analgesic and dose(mg)	Number of patients in comparison	Percent with atleast 50% pain relief	NNT	Lower confidence interval	Higher confidence interval
Etoricoxib 180/240	280	77	**1.5**	1.3	1.7
Etoricoxib 120	500	70	**1.6**	1.5	1.8
Diclofenac 100	545	69	**1.8**	1.6	2.1
Celecoxib 400	298	52	**2.1**	1.8	2.5
Paracetamol 1000+codeine 60	197	57	**2.2**	1.7	2.9
Rofecoxib 50	675	54	**2.3**	2.0	2.6

Aspirin 1200	279	61	**2.4**	1.9	3.2
Ibuprofen 400	5456	55	**2.5**	2.4	2.7
Oxycodone IR 10+ paracetamol 650	315	66	**2.6**	2.0	3.5
Diclofenac 25	502	53	**2.6**	2.2	3.3
Ketorolac 10	790	50	**2.6**	2.3	3.1
Naproxen 400/440	197	51	**2.7**	2.1	4.0
Piroxicam 20	280	63	**2.7**	2.1	3.8
Lumiracoxib 400	370	48	**2.7**	2.2	3.5
Naproxen 500/550	784	52	**2.7**	2.3	3.3
Diclofenac 50	1296	57	**2.7**	2.4	3.1
Ibuprofen 200	3248	48	**2.7**	2.5	2.9
Pethidine 100(IM)	364	54	**2.9**	2.3	3.9
Tramadol 150	561	48	**2.9**	2.4	3.6
Morphine 10(IM)	946	50	**2.9**	2.6	3.6
Naproxen 200/220	202	45	**3.4**	2.4	5.8
Ketorolac 30(IM)	359	53	**3.4**	2.5	4.9
Paracetamol 500	561	61	**3.5**	2.2	13.3
Celecoxib 200	805	40	**3.5**	2.9	4.4
Ibuprofen 100	495	36	**3.7**	2.9	4.9
Paracetamol 1000	2759	46	**3.8**	3.4	4.4
Paracetamol 600/650+codeine 60	1123	42	**4.2**	3.4	5.3
Paracetamol 650+ dextropropoxyphen (65mg hydrochloride or 100mg napsylate)	963	38	**4.4**	3.5	5.6
Aspirin 600/650	5061	38	**4.4**	4.0	4.9
Paracetamol 600/650	1886	38	**4.6**	3.9	5.5
Ibuprofen 50	316	32	**4.7**	3.3	8.0
Tramadol 100	882	30	**4.8**	3.8	6.1
Tramadol 75	563	32	**5.3**	3.9	8.2
Aspirin 650+codeine 60	598	25	**5.3**	4.1	7.4
Paracetamol 300+codeine 30	379	26	**5.7**	4.0	9.8
Tramadol 50	770	19	**8.3**	6.0	13.0
Codeine 60	1305	15	**16.7**	11.0	48.0
Placebo	>10,000	18	**N/A**	N/A	N/A

Table 1: The Oxford League Table Of Analgesic Efficacy. [7] (Adapted with permission from bandolier)

Various Scales Used For Measurement of Pain in Post-Operative Setup

Visual analogue scale

It is simple and most common scale used in pain assessment. It consists of a 10 cm line with two anchor points of 'no pain' and 'worst pain imaginable' which is self-assessed by patient. [8]

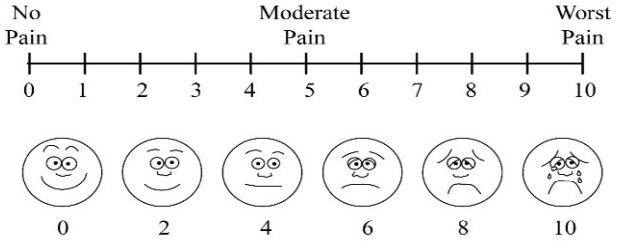


Fig 4: Visual Analogue Scale [9]

Numerical Rating Scale

This scale is similar to the VAS with the two anchors of 'no pain' and 'worst pain as from 0 to 10 which is self-assessed by the patient. [8]

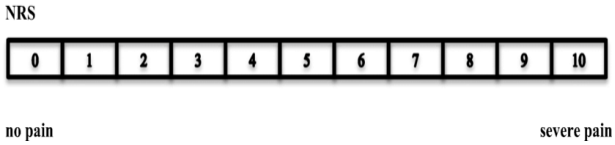


Fig 5: Numerical Rating Scale. [10]

MATERIALS AND METHODS

This is a prospective randomized observational study carried out for a period of 6 months (August 2021 to January 2022) in the Department of Anaesthesiology in Aster Prime hospital, Ameerpet, Hyderabad, Telangana, India. A total of 120 patients who have undergone orthopaedic and general surgeries are selected. The patients are divided into 3 groups of 40 patients each, ketorolac group (group 1), paracetamol group (group 2), and tramadol group (group 3). The patients were administered with desired doses of drugs and the subsequent data was collected in the patient data collection form. Pain onset time, time of first analgesic given, duration of analgesia, haemodynamic parameters were collected from pre-anaesthetic evaluation form and anaesthesia form, OT data collection form, treatment chart and interviewing the patient during follow up. Assessment of pain score was done based on visual analogue scale and numerical rating scale at 2h, 6h, 12h and 24 hours. Median time to rescue analgesic and pain free interval after first dose of analgesic was also assessed. The rescue analgesic Diclofenac 75mg IV was administered when VAS was more than 4 for >2 hours. The statistical analysis was done using Chi-square test.

Inclusion criteria

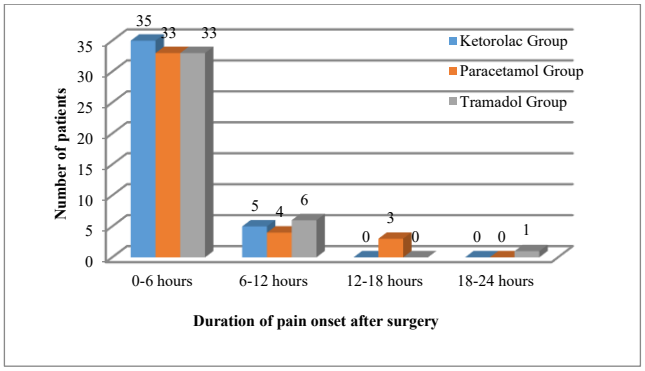
- Both male and female inpatients for general and orthopedic surgeries
- Patients aging between 12-75 years.
- Patients of ASA grade I, II.

Exclusion criteria

- Patients below 12 and above 75 years of age
- Patients of ASA grade > II
- Contraindicated patients (patients with bleeding disorders, dyscrasias, recent history of Myocardial Infarction, Angina, Congestive heart failure, Cerebrovascular accident, Transient ischemic attack, CAD/stents, shock, sepsis, pulmonary diseases, neurological disorders (<3months))
- Patients Allergic to study drugs
- Patients with severe renal or hepatic impairment.

RESULTS AND DISCUSSION

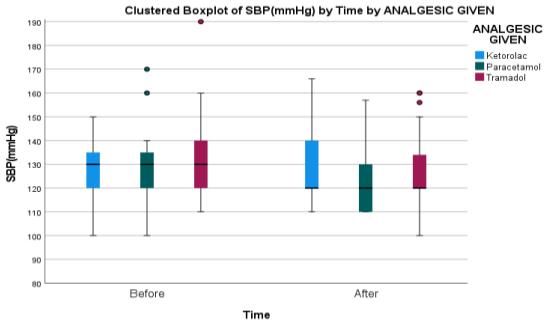
Among the three groups, 87.5% patients (n=35) of group 1 and 82.5% patients (n=33) of group 2 and 3 showed pain onset within 0 to 6 hours followed by 12.5% patients (n=5) of group 1, 10% (n=4) of group 2 and 15% (n=6) of group 3 who showed pain onset within 6 to 12 hours. Three patients of group 2 showed pain onset within 12 to 18 hours followed by 1 patient in group 3 within 18 to 24 hours as shown in graph 1. Chi square test statistic value is 8.479 (P value > 0.05). Hence the difference was statistically insignificant.



Graph 1: Duration of Pain Onset after Surgery

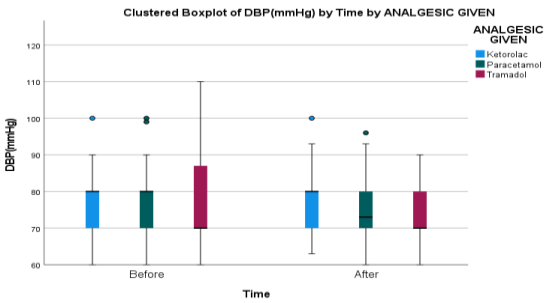
Hemodynamic Parameters

Baseline haemodynamic parameters were comparable in all three groups in which a slight rise in systolic blood pressure (SBP) was found in group 1 as shown in graph 2. A fall in SBP was noted in 9 patients of group and maximum patients of group 2. A statistical significant difference ($P < 0.05$) was found for SBP in group 1 and group 2.



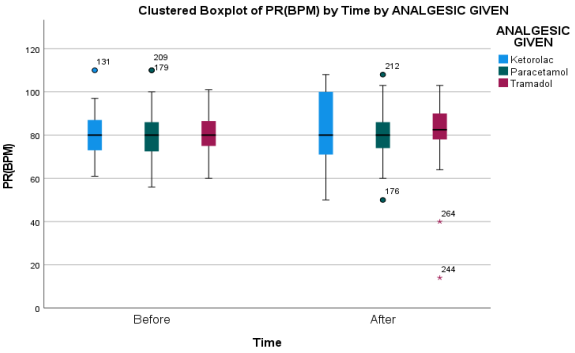
Graph 2: Systolic Blood Pressure

As shown in graph 2, in group 3, a decrease in DBP after surgery was noted. However, the difference in diastolic blood pressure (DBP) was statistically insignificant.



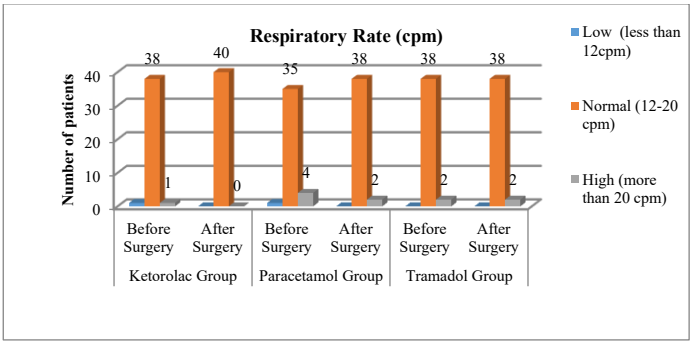
Graph 3: Diastolic Blood Pressure

The incidence of tachycardia was more in group 1 after surgery as shown in graph 4.



Graph 4: Pulse Rate

No statistically significant difference was observed in respiratory rate, temperature and oxygen saturation (SpO2%) as shown in graph 5, table 2 and 3 respectively.



Graph 5: Respiratory Rate

Table 2: Body Temperature (F) of patients with respect to Analgesic given

Body Temperature (F)	Ketorolac Group		Paracetamol Group		Tramadol Group	
	Before Surgery	After Surgery	Before Surgery	After Surgery	Before Surgery	After Surgery
Hypothermia (<95)	0	0	0	0	0	0
Normal (97.0-99.5)	40	40	40	40	40	40
Fever (99.6-100.9)	0	0	0	0	0	0

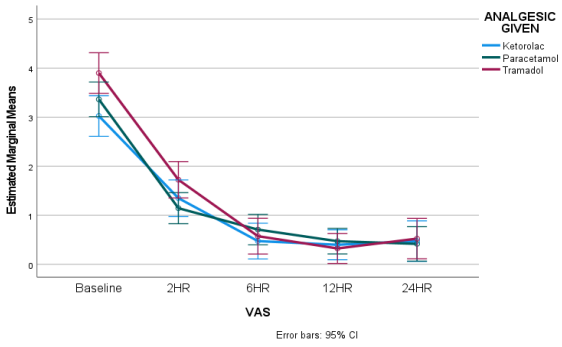
Hyperthermia (101-103.9)	0	0	0	0	0	0
Hyperpyrexia (>104)	0	0	0	0	0	0

Table 2: Body Temperature (F)

Table: Oxygen saturation (SpO2 %)of patients with respect to Analgesic given						
Oxygen saturation (SpO2 %)	Ketorolac Group		Paracetamol Group		Tramadol Group	
	Before Surgery	After Surgery	Before Surgery	After Surgery	Before Surgery	After Surgery
≤60%	0	0	0	0	0	0
61%-70%	0	0	0	0	0	0
71%-80%	0	0	0	0	0	0
81% - 90%	0	0	1	0	0	0
>90%	40	40	39	40	40	40

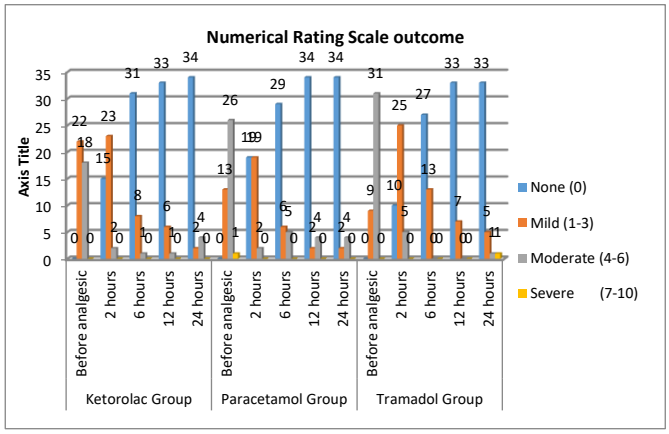
Table 3: Oxygen Saturation (SpO2 %)

The VAS score was evaluated in three groups and it showed that at 2 hours after administration of analgesic, the pain reduction was maximum in group 2 whereas, group 1 showed maximum pain reduction at 6 hours. One patient in group 1 and 5 patients in group 2 showed moderate pain at 6 hours. Pair comparisons showed that group 1 showed maximum pain reduction followed by group 2. The pain reduction was least in group 3 as shown in graph 6.



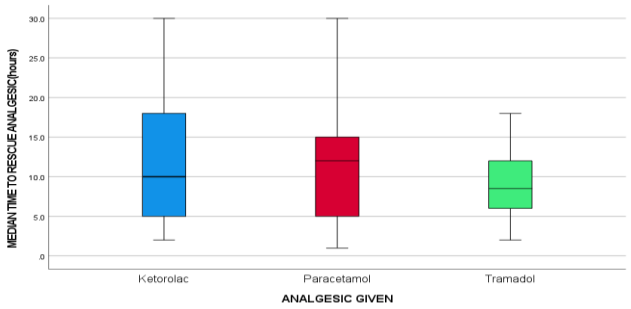
Graph 6: Visual Analogue Scale

The NRS score was evaluated in three groups and it showed that at 2 hours after administration of analgesic, the pain reduction was maximum in group 2 whereas, group 1 showed maximum pain reduction at 6 hours. One patient in group 1 and 5 patients in group 2 showed moderate pain at 6 hours. Pair comparisons showed that group 1 showed maximum pain reduction followed by group 2. The pain reduction was least in group 3 as shown in graph 7.



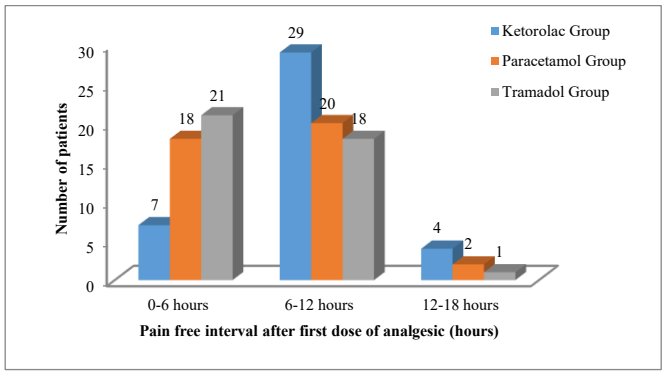
Graph 7: Numerical Rating Scale

The rescue analgesic given was INJ. DYNAPAR (Diclofenac) 75mg IV if the pain score was more than 4 for >2 hours. The requirement of rescue analgesic was highest in group 1 followed by group 3 as shown in graph 8. The requirement for rescue analgesic at 0-6 hours and 6-12 hours duration was highest in group 3 followed by group 1. Average of median time to rescue analgesic was highest for group 1 (8.7) followed by group 3 (5.7).



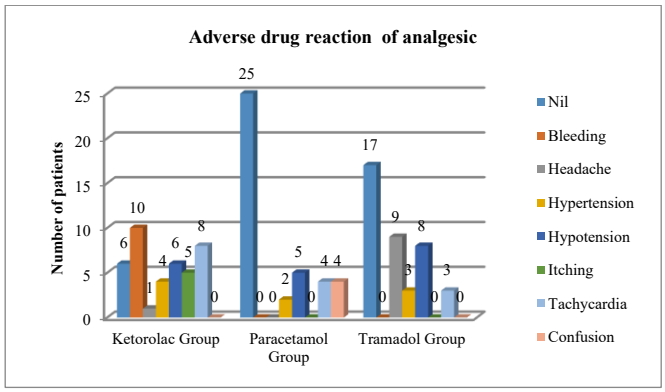
Graph 8: Median Time to Rescue Analgesic

Patients of group 1 (n=29) had a pain free interval ranging from 6-12 hours. The shortest duration of pain free interval was found in group 3 (n=21) ranging between 0-6 hours. Four patients of group 3 had pain free interval ranging between 12-18 hours as shown in graph 9. The average of pain free interval was highest in group 1 (10.25) followed by group 2 (8.4).



Graph 9: Pain Free Interval After First Dose Of Analgesic (hours)

The incidence of adverse drug reactions were highest in group 1 with more cases of bleeding (n=10), Tachycardia (n=8) and hypotension (n=6). 9 patients in group 3 reported headache as shown in graph 10.



Graph 10: Adverse Drug Reactions of Analgesics

CONCLUSION

This study concludes that ketorolac has more efficacy than that of paracetamol in reduction of post-operative pain in orthopedic and general surgeries. Three drugs were compared for their efficacy post-operatively using VAS and NRS at 2h, 6h, 12h and 24h after administration of analgesic. Ketorolac was found to have more efficacy than that of paracetamol in terms of pain reduction. The average of median time to rescue analgesic was highest in ketorolac group which proves greater post-analgesic efficacy. The average of pain free interval was also highest in ketorolac group. However, the incidence of adverse drug reactions was more in ketorolac group. Hence, it is concluded that ketorolac when given post-operatively is a more effective analgesic when compared with paracetamol and tramadol as it gives a longer duration of analgesia which decreases the use of rescue analgesic.

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