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Comparison of Analgesic Efficacy of Diclofenac Sodium, Ketorolac and Tramadol after Laparoscopic Cholecystectomy

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ABSTRACT

The aim of this study was to compare the analgesic efficacy of diclofenac sodium, ketorolac, tramadol individually and their combination after laparoscopic cholecystectomy. Total 150 subjects who met the inclusion and exclusion criteria were randomly (lottery method) divided into five groups to receive respective treatment. Pain score was measured after 1, 2, 4, 6, 12, 24 and 48 hours after surgery through visual analogue scale. The data was statistically analyzed through SPSS (version 20.0). It is concluded on the basis of collected results that a combination of Non-Steroidal Anti-inflammatory Drugs and Opioid derivatives is much superior to achieve effective pain control than either of the drug alone. Furthermore, ketorolac and tramadol combination provided more efficient pain control than diclofenac sodium and tramadol combination. This effective pain control is associated with short hospital stay which will cause less economic burden for patients. So, we may recommend that Non-Steroidal Anti-inflammatory Drugs (ketorolac) and opioids (tramadol) combination should be used for effectual pain control after laparoscopic cholecystectomy.

Keywords: Diclofenac, Ketorolac, Tramadol, Cholecystectomy.

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INTRODUCTION

Postoperative Pain (PP) is a typical gripe which restricts tolerant development, solace and deferral release from clinic. Pain is more than only a physical procedure; it is an intricate, subjective sensation[1]. An endless number of pain relievers are accessible and promptly regulated to control pain in post-surgical patients. Most generally utilized analgesics incorporate opiates and Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Diclofenac is an old, time tried pain relieving drug. It can be administered through IM (most regular), IV (in weakened structure), oral and per-rectal route. Provocative issue may incorporate musculoskeletal grumblings, particularly polymyositis, dermatomyositis, osteoarthritis, joint inflammation, rheumatoid joint inflammation, dental pain, spondyl-joint inflammation, ankylosing spondylitis, gout assaults, and pain administration in instances of gallstones and kidney stones. Diclofenac is accessible in distinctive structures diclofenac sodium (DS), diclofenac potassium and diclofenac acid. Most normal unfriendly impact of DS is gastritis, impeded renal capacity, platelet breaking down and debilitated coagulation. Diclofenac is among the better-endured NSAIDs. Ketorolac (KE) is additionally a NSAID utilized as a pain relieving. KE acts by hindering the substantial amalgamation of prostaglandins. The essential component of activity in charge of KE's mitigating antipyretic and pain relieving impacts is the hindrance of prostaglandin combination by focused obstructing of the compound COX. KE is a non-particular COX inhibitor[2]. KE is not prescribed for PP control or co-organization with anaesthesia on the grounds that it represses platelet conglomeration and consequently may be connected with an expanded danger of dying. KE is not suggested for obstetric absence of pain in light of the fact that it has not been enough tried for obstetrical organization and has obvious fetal toxicity in research center modeling. KE is not suggested for long haul interminable pain patients. Similarly as with all NSAIDs, KE ought to be dodged in patients with renal failure. The patients at most elevated danger, particularly in the elderly, are those with liquid uneven characters or with traded off renal capacity (e.g., heart abnormalities, diuretic utilization, cirrhosis, drying out, and renal deficiency) Tramadol (TD) will be a engineered, halfway acting atypical oral opioid which acts by blocking neuronal reuptake of norepinephrine and serotonin[3]. TD goes about as a μ-opioid receptor agonist[4, 5], serotonin discharging operators[6], norepinephrine reuptake inhibitor, NMDA receptor antagonist[7], 5-HT_{2C} receptor antagonist, (α7)5 nicotinic acetylcholine receptor rival, TRPV1 receptor agonist, and M_1 and M_3 muscarinic acetylcholine receptor opponent[8, 9]. TD has inhibitory activities on the 5-HT_{2C} receptor. It is regularly joined with paracetamol (PCM) as this

is known not the adequacy of TD in alleviating pain. TD is an atypical opioid on the grounds that it is a SNRI of and, without anyone else, a genuinely feeble μ-opioid receptor agonist. TD is metabolized to O-desmethyltramadol, which is an altogether more powerful opioid with extra norepinephrine reuptake-restraining properties, making it comparable to tapentadol[10]. TD seems to have the same adequacy as the mix of codeine and PCM. However, dissimilar to others, it will be related with fundamentally less respiratory misery and has little impact on gastric purging. A study demonstrated that utilization of NSAID before operation may have more gainful that after surgery[11], comparatively opioid are additionally more successful if given before as opposed to after operation[12]. Its pain relieving impacts take around 1 hr to go live and 2 to 4hrs to crest after oral organization with a prompt discharge detailing. The most well-known unfavorable impacts of TD incorporate queasiness, discombobulating, dry mouth, heartburn, stomach pain, vertigo, retching, clogging, sluggishness and cerebral pain[13]. Compared to different opioids respiratory dejection and stoppage is viewed as to a lesser extent an issue with TD[14]. Cholecystectomy (CST) is the surgical evacuation of the gallbladder. It is a typical treatment of symptomatic gallstones and other gallbladder conditions. Surgical choices incorporate the standard system, called laparoscopic cholecystectomy, and a more seasoned more intrusive method, called open CST. Laparoscopic CST is the highest level treatment for symptomatic cholilithiasis and a standout amongst the most ordinarily performed elective surgical system. Evidences for CST incorporate aggravation of the nerve bladder (cholecystitis), biliary colic, danger components for nerve bladder tumor, and pancreatitis created by nerve stones. The most genuine difficulty of CST is harm to the basic bile conduit. This happens in around 0.25% of cases. Harm to the channel that causes spillage regularly shows as fever, jaundice, and stomach pain a few days taking after CST. A slashed, broken bile conduit might be repaired through a technique called ERCP, or endoscopic retrograde cholangiopancreatography.

MATERIALS AND METHOD

Subjects

Informed consent was taken from the patients. Subjects were asked about the previous history of the drugs intake and any previous adverse effect. Subjects were explained to inform if they experience any of the adverse reaction of the drug. In case, this will be documented. Patients were followed till 48 hrs after surgery or discharge whichever occurs first. Subjects were explained in detail about the possible effects and adverse reactions of both drugs from which one of the drugs were given to them.

Ethical considerations

The study was approved by the Ward Committee (Surgical Unit I, Jinnah Hospital, Lahore) and by similar committees at all other participating sites. Patients were screened and 150 were randomly selected according to predefined inclusion and exclusion criteria, then written informed consent was obtained.

Protocol design

This study is a single centered randomized blind trial. Total 150 patients were enrolled, divided into five equal groups (n=30), each group received medications as shown in table 1. Pain was measured at 1, 2, 4, 6, 12, 24 and 48 hrs after surgery through Visual analogue scale. Inclusion Criteria: Patients who underwent elective laparoscopic CST were included in the study above the age of 13 years. Exclusion Criteria: Patients who have known hepatic or renal impairment were excluded from the study. Patients who develop adverse drug reaction were also excluded from the study. Patients who have any known contraindication, previous adverse reaction or new onset adverse reaction to any of the drug received a change of treatment as appropriate.

Sampling techniques

Simple random sampling technique was used to select the patients. Random patients were selected from the elective surgical list day before the surgery. Statistical analysis was done on SPSS (version 20.0). Demographic variable was analyzed and Chi-square test was applied as a test of significance to compare outcome in the patients.

RESULTS AND DISCUSSION

A total of 150 patients were included in this study divided into five groups of 30 patients each. Mean age of patients was 48.33 ± 5.48 years. Minimum age was 32 and maximum age was 60 years. Mean hospital stay was 1.39 ± 0.48 years with range of 1-2 days. Females comprised of about 123 (85.3%) of the study population. In this study, female patients' outnumbered male patients with female to male apportion of 5.5:1, which is in accordance with occurrence of laparoscopic CST in a UK healing center that was 4.5:1. This could be because of expanded number of male populace experiencing laparoscopic CST. Cholelithiasis is basic in fat, ripe, forty, heavy female[15]. Occurrence of cholelithiasis is expanded in inborn heart infection, hyperparathyroidism, thalassemia and other hemolytic sickliness patients[16-18]. A survey of laparoscopic CST demonstrated that there will be enhanced clinical result and lessened monetary trouble a great many laparoscopic CST[19]. In this study, mean age of the patients was 48.33 ± 5.48years. Similarly, a study from Jamaica demonstrated mean age at conclusion of cholelithiasis

that was 47 years. Cholelithiasis is unprecedented in pediatric and geriatric populace[20]. Mean pain score of all groups was 4.56 ± 0.815, 4.28 ± 0.696, 3.33 ± 0.730, 2.78 ± 0529, 2.49 ± 0.621, 2.08 ± 0.681, 1.40 ± 0.645 at 1, 2, 4, 6, 12, 24 & 48 hrs respectively as shown in table no. 2. The table represents overall mean score of all groups with maximum pain score of 4.56 at 1 hr after surgery which reduced to 1.4 at 48 hrs after surgery. This signifies that pain score in all groups is reduced due to medication. This also means all drugs are effective in reducing pain. A Cochrane survey on pharmacological mediation reported that pain score on visual simple scale decrease by 1 or 2, 4 to 8 hrs after surgery. In this survey both non-steroidal, opioid analgesics and against convulsant medications were directed for pain control[21]. In our study comparable pattern was watched where mean pain score lessened from 4.56 at 1 hr to 2.49 at 8 hrs. An investigation of 100 patients demonstrated that pain score was under 4 in all instances of laparoscopic CST at unsurpassed. In our study, mean greatest pain many laparoscopic CST whenever was 4.5 which is marginally more than reported by Jimenez. A study reported pain at 8 hrs 3.5 ± 0.5 and at 24 hrs 3.2 ± 0.4[22]. Lee reported normal pain score of 6.5 after laparoscopic CST. In our study pain at 24hrs was 2.08 ± 0.681 which is somewhat lower. Hussain reported that females' patients have higher pain score than male patients[23]. Uchiyama reported that females have higher pain and body temperature than guys after laparoscopic CST[24]. Mean hospital stay was 1.39 ± 0.48 years with range of 1-2 days. Almost 92 (61.3%) of patients were discharged within first day while remaining 58 (38.7%) patient were discharged between 24-48hrs. Frequency of pain score in each group after 1hr is shown in figure 2. Mean pain score was highest in DS group while lowest in TD group after 1 hr. P < 0.369 which is not significant. This study demonstrated that at 1 hr mean pain score after combination TD and DS utilization was 2.4 ±1.5. Another study demonstrated that preanesthesia organization of DS organization diminishes pain score 2-6 hrs after surgery[25]. Durak reported mix of PCM and opioids is better than combination of DS and opioids as respect to pain control and unfavorable impacts[26]. In our study TD and KE gave more productive pain control at all times after surgery than in DS and TD bunch. Wilson demonstrated that combination of DS with opioids is better than opioids alone in accomplishing pain help after laparoscopic CST[27]. Frequency of pain score in each group after 2 hrs is shown in figure 3. Pain was most in DS group while minimum in KE & TD combination group. Mean pain score was 4.57 for DS group while 4.03 for group V. P value was not significant (p=0.113).Frequency of pain score in each group after 4 hrs is shown in figure. 4. Patient in tramadol group complained of pain most after 4 hrs, mean pain score was 3.33 while lowest mean pain was observed in DS and tramadol group which was 2.67. The p-value was significant (p <0.000).Frequency of pain

score in each group after 6 hrs is shown in figure .5. Maximum pain was in tramadol group with mean pain score of 2.97 while minimum pain was reported in ketorolac & tramadol group with mean pain score of 2.4. P value was significant (p<0.000).Abdullah reported NSAIDS alone lessen pain essentially just 24 hrs after laparoscopic CST[28]. In our study pain score was diminished to half in both DS and KE bunch. Matkap *et al*. reported that pain score was 6 with in 1st hr after laparoscopic CST for patient getting TD just[29]. In our study pain score in TD bunch at 6 hrs was 2.97 which is half than the investigation of Matkap. Durak reported opioids will be better than DS for PP control after laparoscopic CST[26]. In our study TD gave more proficient pain control at all times after surgery than in DS bunch. Frequency of pain score in each group after 12 hrs is shown in figure 6. Best pain control was achieved in ketorolac and tramadol group with mean pain score of 1.77. Comparatively minimum pain control was achieved in DS group with mean pain score of 2.93. P value was significant (p < 0.000). Frequency of pain score in each group after 24 hrs is shown in figure 7. Pain was more in Diclofenac sodium group and least in ketorolac and tramadol group, p value was < 0.000. Frequency of pain score in each group after 48 hrs is shown in figure 8. Maximum pain was reported in DS group while least pain was reported in ketorolac and tramadol group, p value was < 0.000.KE is connected with gastrointestinal discharge and postponed coagulation after laparoscopic CST[30, 31]. A study demonstrated that NSAIDS indomethacin and KE are just as powerful in control of post-agent pain after laparoscopic CST[32]. Ekmecki demonstrated that mix of TD with KE is more powerful than TD alone for post laparoscopic CST pain[33]. In this study pain score at 2, 4, 6, 12 and 24 hrs was altogether lower for combination bunch. Mean score for combination groups was 3.5, 3, 2.5, 2 and 1.5 for TD groups while 3, 2.7, 1.8, 1 and 0.5 was observed for mix bunch at 2, 4, 6, 12 and 24 hrs individually. A study distributed in 2009 demonstrated that TD may be provider intraperitoneally for pain control after laparoscopic CST[34]. Akinci decided intravenous TD is unrivaled in accomplishing early post laparoscopic CST pain control[35]. Gopalraj demonstrated that KE is better than TD in accomplishing pain control in initial 8 hrs after surgery[36]. Shankariah indicated diverse results; his study results demonstrated that TD is more viable than KE for pain control from 2-24 hrs after surgery[37]. Ali reported that TD is more viable than KE for pain control after day case laparoscopic surgery[38]. Pieri reported TD and KE mix is powerful in PP control after real stomach surgery, very still greatest pain score was 3 and on development was 4[39]. Olle demonstrated that mean pain score after stomach hysterectomy for patient getting TD was 3.6 while 4.4 for KE bunch[40]. Hospital stay of each group is shown in table no. 3. Patients in DS group had a longer hospital stay period than all other groups. P value was 0.194

which is not significant. Mean pain score in each group over time is shown in figure 9. Pain score was highest in Diclofenac sodium group and lowest in ketorolac and tramadol group at all times. It is concluded from the results of our study that a combination of NSAIDs and Opioid derivatives is superior to achieve pain control than either of the drug alone. It is further concluded that a combination of KE and TD provides more efficient pain control than the combination of DS and TD. Effective pain control is associated with short hospital stay. Therefore, we may recommend that a combination of opioids (TD) and a NSAID (KE) should be used for pain control after laparoscopic CST.

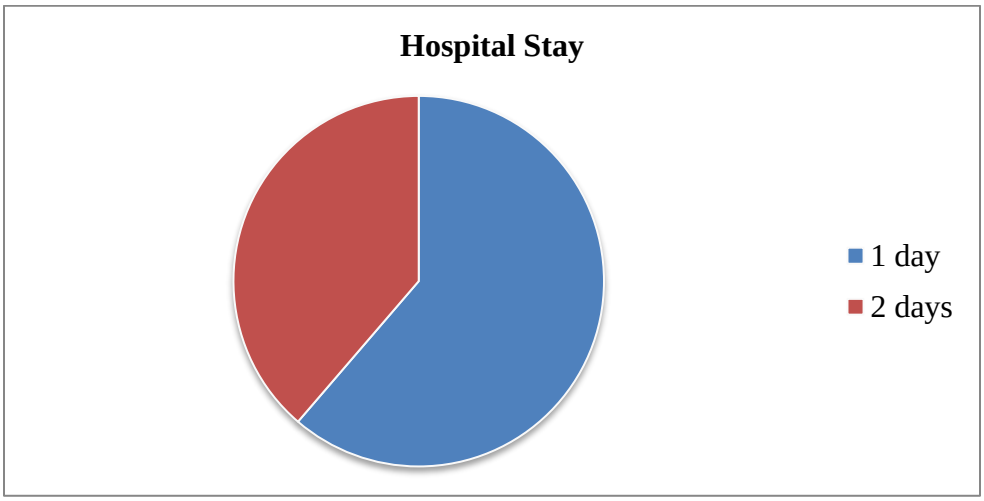

Figure .1: Pie chart showing hospital stay. The figure shows the stay time of patients in hospital after the surgery. Total 61.3% of patients discharged within first day while 38.7% were discharged between 24-48 hrs.

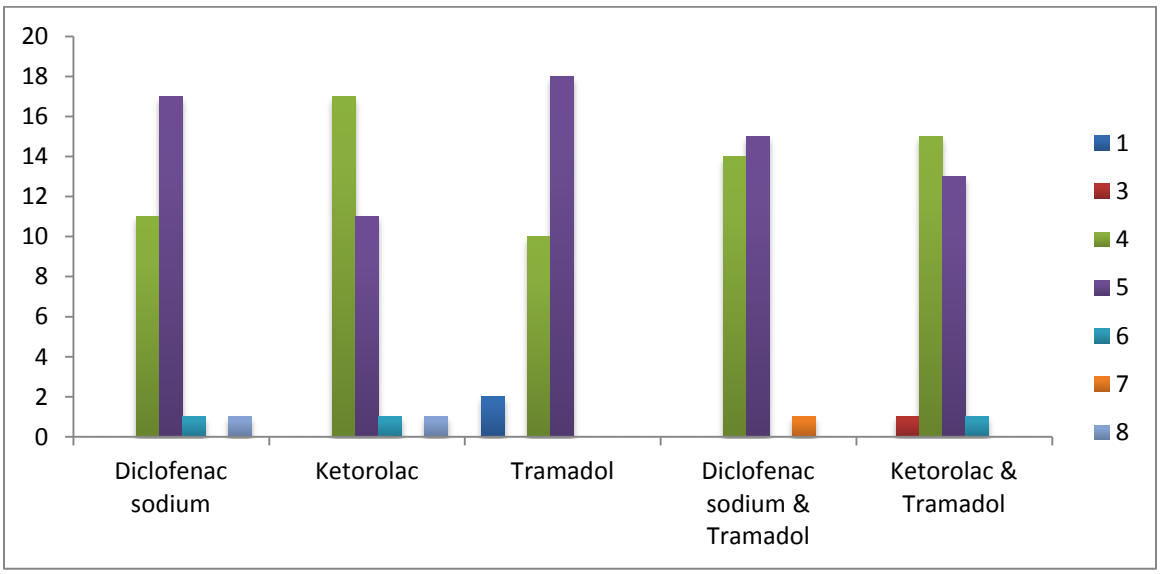

Figure 2: Pain score 1 hour after surgery. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

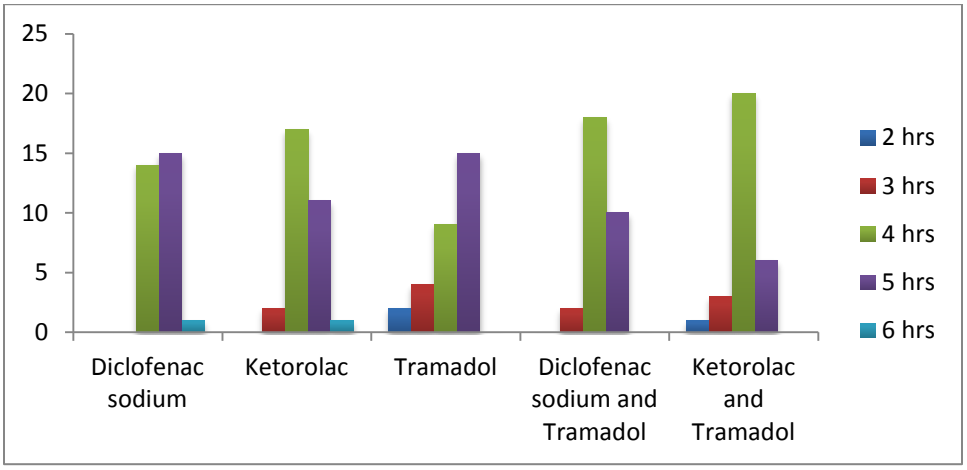

Figure 3: Pain score 2 hrs after surgery. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

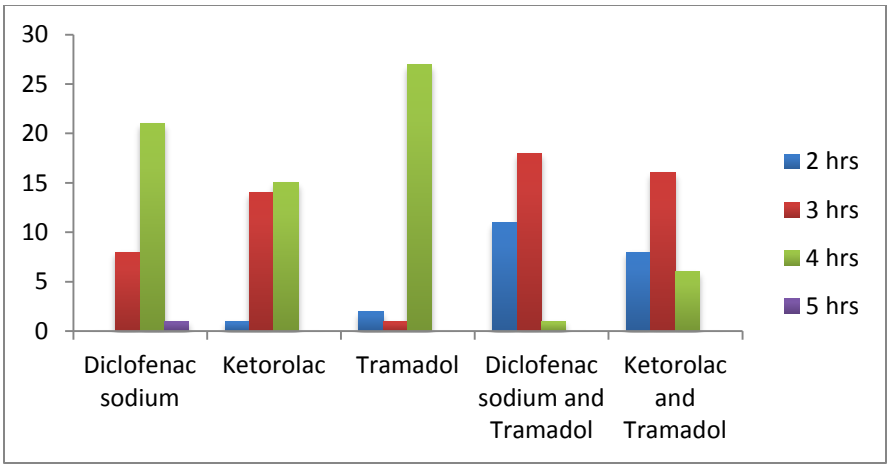

Figure 4: Pain score 4 hrs after surgery. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

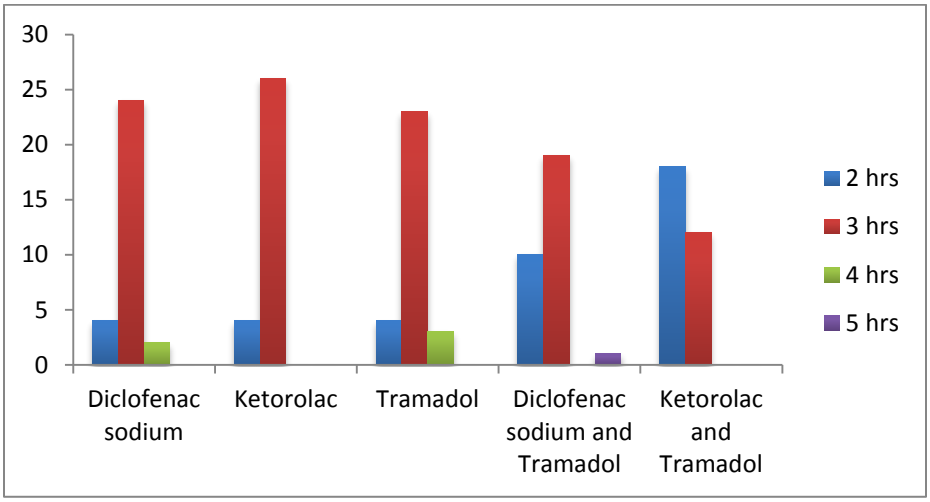

Figure 5: Pain score 6 hrs after surgery. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

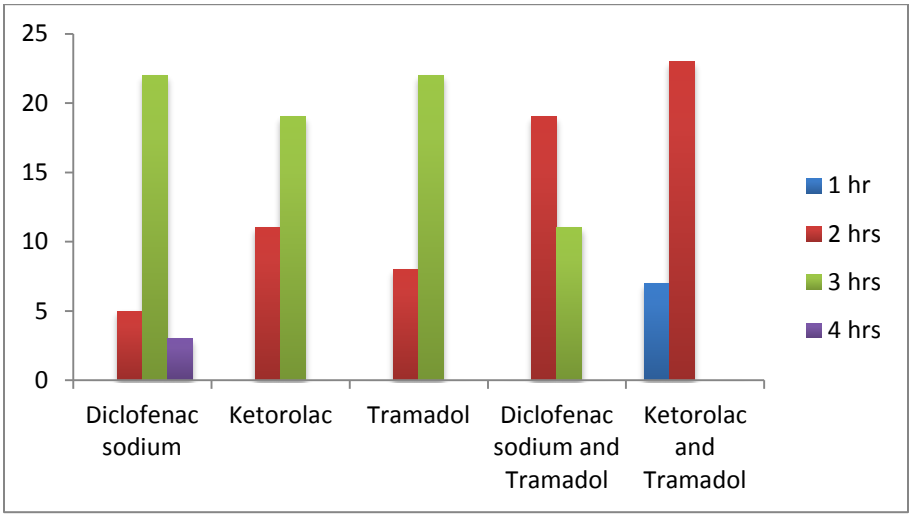

Figure 6: Pain score 12 hrs after surgery. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

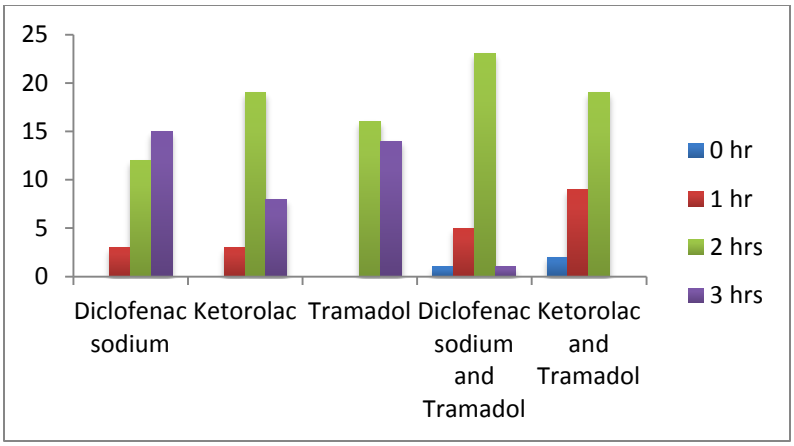

Figure 7: Pain score 24 hrs after surgery. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

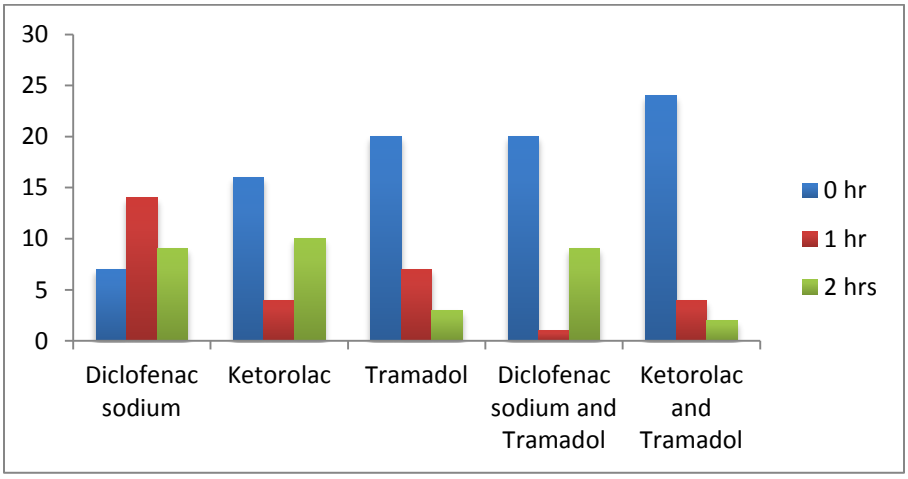

Figure 8: Pain score 48 hrs after surgery. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

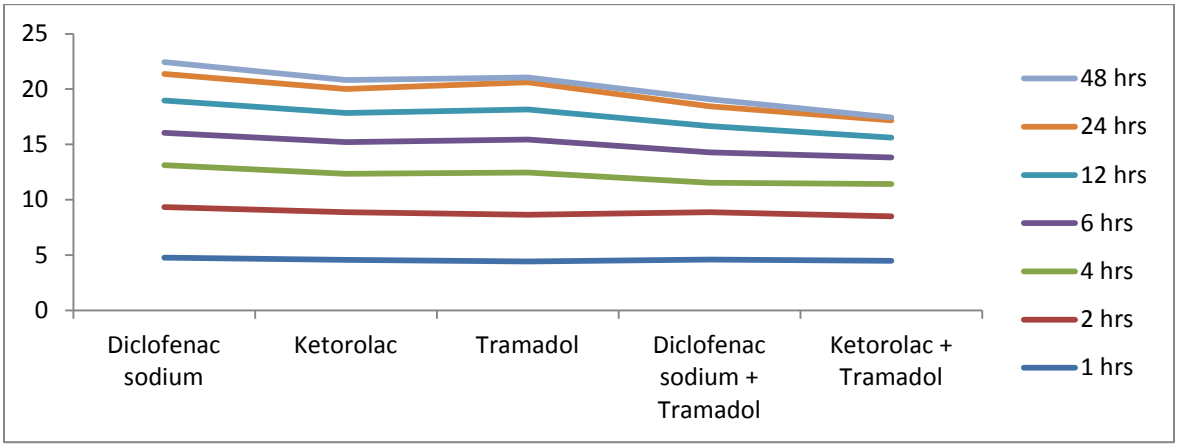

Figure 9: Mean pain score overtime in each group. X-axis shows number of patients while y-axis shows frequency of patient with their pain score

Table 1: Experimental Groups with their Respective Treatment

Group	Treatment	No of Patients	Dosage	Total Dose IM	Recommended dose
Group-I	Diclofenac sodium	30	75mg/3ml	75mg/3ml BID for	150mg
Group-II	Ketorolac	30	30mg/1ml	30mg/ml BID for	60mg
Group-	Tramadol	30	50mg/ml	50mg/ml BID for	100mg
Group-	Diclofenac sodium + Tramadol	30	-	37.5mg/1.5ml +	-
Group-	Ketorolac + Tramadol	30	-	15mg/0.5ml +	-

Table 2: Mean Pain Score Over Time

Time interval (hrs)	Mean pain Score
1	4.56 ± 0.815
2	4.28 ± 0.696
4	3.33 ± 0.730
6	2.78 ± 0.529
12	2.49 ± 0.621
24	2.08 ± 0.681
48	1.40 ± 0.645

Table 3: Hospital Stay in Each Group

Group	1 day	2 days	Total Patients
Diclofenac sodium	14	16	30
Ketorolac	16	14	30
Tramadol	20	10	30
Diclofenac sodium +Tramadol	20	10	30
Ketorolac + Tramadol	22	8	30
Total	92	58	150

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