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RESEARCH ARTICLE

"COMPARISON OF PRE-EMPTIVE PARACETAMOL AND PARACETAMOL-DICLOFENACCOMBINATION FOR POSTOPERATIVE PAIN AFTER SURGERIES UNDER GENERAL ANESTHESIA - A SINGLE-BLINDED RANDOMIZED CONTROL STUDY"

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Abstract

Background: Postoperative pain control is a critical component of patient care. Effective pain control can improve patient comfort and reduces the risk of complications. Multimodal analgesia is one of the approaches used for postoperative pain control. The idea of combining analgesics is to reduce the side effects of each drug yet effectively deal with postoperative pain. The present study aimed to compare the time for the first analgesia request and compare the total amount of analgesic consumption in the two groups in the postoperative period in the first 24 hrs.

Methods: The present study was a single-blinded randomized control study, done in the Department of Anesthesiology, MRMC, and Basaveshwar Teaching and General Hospital, Kalaburgi, Karnataka State. Patients undergoing surgeries under General Anaesthesia with ASA I/II categories were randomly allocated to two groups. Group A n=25 patients with Tab. Paracetamol oral(2gm). Group B n=25 patients with Tab. Paracetamol oral(1gm). + Inj Diclofenac 75mg IM. Postoperative NRS and first demand for rescue analgesia and total consumption of analgesic in two groups were compared.

Results: The mean values of NRS scores were found to be lesser in group B as compared to group A indicating better pain control in group B as compared to group A. The time for 1st analgesia request was seen in 60% of group A in 2nd hour and 32% in 1st hour. Time for 1st analgesia request was seen in 60% of patients in group B in the 3rd hour and 20% in the 2nd hour. The overall consumption of analgesics at the end of 24 hours was greater in Group A as compared to Group B.

Conclusion: Pre-emptive analgesia with inj. diclofenac is more effective when compared to a tab. paracetamol group alone in post-operative analgesia following elective surgeries. It can further improve the quality of multimodal analgesia during the post-operative period and can reduce the hospital stay and financial burden on the patient. Both paracetamol and diclofenac drugs are safe to provide analgesia in the postoperative period without any major significant side effects.

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Introduction:-

According to International Association for theStudy of Pain (IASP), defines pain as"unpleasant emotional and sensory experience due to actual or potential tissue damage".[1] Studies show that a substantial number of patients have moderate to severe pain following surgeries in the immediate and early postoperative phases. [2, 3]Poorly controlled postoperative pain can have a significant impact on a patient's health on many levels, including hypertension, myocardial ischemia, arrhythmias, respiratory problems, slow wound healing, chronic pain, deep vein thrombosis, and risk for emergence of chronic pain syndrome.[4-6] These detrimental effects result in longer hospital stays and adverse postoperative outcomes. This may impair sleep and have negative psychological effects. [7]One approach to enhance the healing process is the use of multimodal analgesic strategies as the usual way for pain avoidance during surgery. [8, 9] Pre-emptive analgesia, which is one of the components of the multimodal approach used nowadays, is the administration of a painkiller before surgery. Pre-emptive analgesia reduces postoperative pain intensity and lowers the likelihood of postsurgical chronic pain by blocking central nervous system hyperexcitability. [10, 11] It is an antinociceptive medication.

The commonly used analgesic medication is Opioids. They have sedative properties. Nonsteroidal anti-inflammatory drugs (NSAIDs) are advantageous due to their lack of sedative effects and opioid-sparing effects, but their effectiveness is constrained by side effects like nausea, vomiting, and phlebitis at the injection site. [12] as well as relative contraindications like known drug hypersensitivity, allergic asthma, kidney disorders, and acid peptic disorder.[13]Diclofenac is the most commonly used drug among NSAIDs. Paracetamol is a centrally acting cyclo-oxygenase inhibitor and is quite safe and effective with minimal side effects as compared to diclofenac especially on IV administration. IV paracetamol has a quite rapid onset of action reasonable durability, good analgesic efficacy, and with least side effects in the dosage commonly used.[14-16]The percentage of patients experiencing moderate to severe pain after surgery has remained stable over the previous ten years. [17, 18] despite this evidence-based strategy to increase perioperative analgesia. As a result, anesthesiologists in developing nations find it more challenging to effectively treat postoperative pain, which creates an opportunity to research more effective interventions that may be used in settings with low resources. Further research is required to determine the best pre-emptive analgesic medicine combined with the fewest adverse effects, as well as one that is accessible, manageable, and inexpensive. [19] In nations with limited means to utilize expensive analgesics. The present study evaluates the combination of medications that are opioid-free analgesic paracetamol and a combination of (paracetamol & diclofenac) with respect to analgesic consumption in two groups in the postoperative period in the first 24 hrs and compares the time for 1st analgesia request in two groups.

Material and Methods:-

The present study was a single-blinded randomized control study, done in the Department of Anesthesiology, MRMC, and Basaveshwar Teaching and General Hospital, Kalaburgi, Karnataka State. Institutional Ethical approval was obtained for the study based on the Helsinki Declaration of 1964 for human subjects involved in biomedical research. Written consent was obtained from all the participants of the study after explaining the nature of the study in vernacular language.

Sample size estimation was done using Open EPi Software Version 2.3.1.At 95% confidence level, and 80% power of the study α(two-tailed) =0.050 and at 95% confidence level.β= 0.200 and 80% of the power of the study. Where Zα=standard table value for 95% CI=1.96. $Z_{1-\beta}$=Standard table value for 80% Power=0.8Based on the previous study by Aweke Z et al., [20]the Sample size is calculated using the formula.

$$n = 2(Z\alpha+Z1-\beta)^2 \sigma^2/d^2$$

The sample size estimated is 22 which is rounded off to 25. Therefore, there will be n=25 patients in each group.

Inclusion Criteria:

1. ASA physical status I and II
2. Age > 18 years.
3. Body mass index ≤30 kg/m^2
4. Patients undergoing surgeries under General Anaesthesia.
5. Voluntarily willing to participate in the study.

Exclusion Criteria:
1. The patient refused to give consent.
2. Co-morbidities like Anaemia, DM, HTN, and Arthritis.
3. Moderate or severe renal impairment (serum creatinine ≥1.6 mg/dl)
4. Known asthmatic patient.

Group A (n=25) patients received Tab. Paracetamol oral (2gm).Group B(n=25) patients with Tab. Paracetamol oral(1gm). + Inj Diclofenac 75mg IM. The participants/patientswere not blinded but the anesthesiologist who is assessing the pain was blinded.

Procedure:At night before the surgery, an oral Tab of Paracetamol (1 g) with sips of water was given to both groups. In the morning, on the day of surgery (60 min before surgery) 1gm of oral Paracetamol (Group A), and 75 mg of intramuscular (IM) Diclofenac were administered to Group B.

Pre-operatively, baseline vital sign, and the presence and severity of pain (NRS for pain) was assessed.Standard monitors were used for all the patients. The standard general anesthesia protocol was employed. Post-operatively pain was assessed by NRS scale by asking patients to self-report pain using an 11-point NRS, a score from 0-10.The NRS score is recorded at recovery after the patient is fully awake from anesthesia, at the end of 1,2,4,8,12, and 24hr by the anesthetist who is blinded to the treatment allocation.24hr post-operative analgesia consumption, time to first analgesia request is recorded. When there was a request for the first analgesia by the patient or the NRS score >4, Inj. Tramadol 50mg IV was given. After 24hrs, postoperative analgesic therapy treatment was continued according to hospital protocol.In case of nausea and vomiting, intravenous metoclopramide 10mg & intravenous dexamethasone 4 mg was given.

Statistical analysis: All the available data was recorded and uploaded on an MS Excel spreadsheet and analyzed using IBM SPSS Software 20.0 in Windows format. Quantitative variables were expressed as mean and standard deviations and qualitative variables were expressed in proportions and percentages. The means of the two groups were compared with Student's t-test. The categorical variables were estimated by chi-square test and values (<0.05) were considered as significant.

Results:-

A total of n=50 cases divided equally between the two groups of n=25 each were included in the study. The most common age group in this study was the age of 41 – 50 years with 40% of all the cases. Followed by the age group of 31 – 40 years with 34% of all cases. Out of the n=25 cases in group A n=11/25 (44%) were males and n=14/25 (66%) were females. Similarly, in group B out of n=25 cases n=12/25 (48%) were males and n=13/25(52%) were females. The age range of group A patients was from 23 years to 65 years. The age range of group B patients was from 24 years to 68 years. The other age-wise distribution of cases is depicted in Table 1.

Table 1:- Age-wise distribution of cases in the study.

Age group	Group A	Group B	Total (%)
21 – 30	03	02	05 (10%)
31 – 40	08	09	17 (34%)
41 – 50	11	12	20 (40%)
51 – 60	02	01	03 (6%)
61 – 70	01	01	02 (4%)
Total	25	25	50 (100%)

The comparison of parameters recorded in two groups was compared to the distribution of cases in groups A and B for males and females the p values were > 0.05 hence it was a uniform distribution of cases in both groups. The mean age of group A was 46.50 ± 13.3 years and group B was 48.06 ± 13.95 years.Based on the ASA I and II category distribution in both groups maximum number of cases in this study were belonging to ASA I category and the rest to the ASA II category. The p values were not significant indicating equal distribution of cases based on ASA categories in both groups. The height, weight, and BMI mean values are depicted in Table 2. All the parameters were not found to be significant hence distribution of all parameters was equal in both groups of the study.

Table 2:- Comparison of parameters recorded in both groups.

	Group A	Group B	P values
Male	11	12	0.756
Female	14	13	0.981
Age	46.50 ± 13.3	48.06 ±13.95	0.214
ASA I	18	20	0.332
ASA II	7	5	0.471
Weight	61.50±5.84	61.13±8.26	0.719
Height	161.70±5.70	158.3±5.34	0.158
BMI Kg/m^2	23.58 ± 0.84	22.9 ± 0.77	0.291

In our study group A (tab. Paracetamol 2 gm oral) received inj. tramadol IV (244 ± 36.28mg)and group B (tab. paracetamol oral 1gm +inj. Diclofenac IM 75 mg) received inj.tramadol IV (156 ± 8.81mg) postoperatively in the First 24 hours. The consumption of postoperative analgesia was significantly higher in group A as compared to group B and the p-value (<0.001) is considered significant and the details depicted in Figure 1.

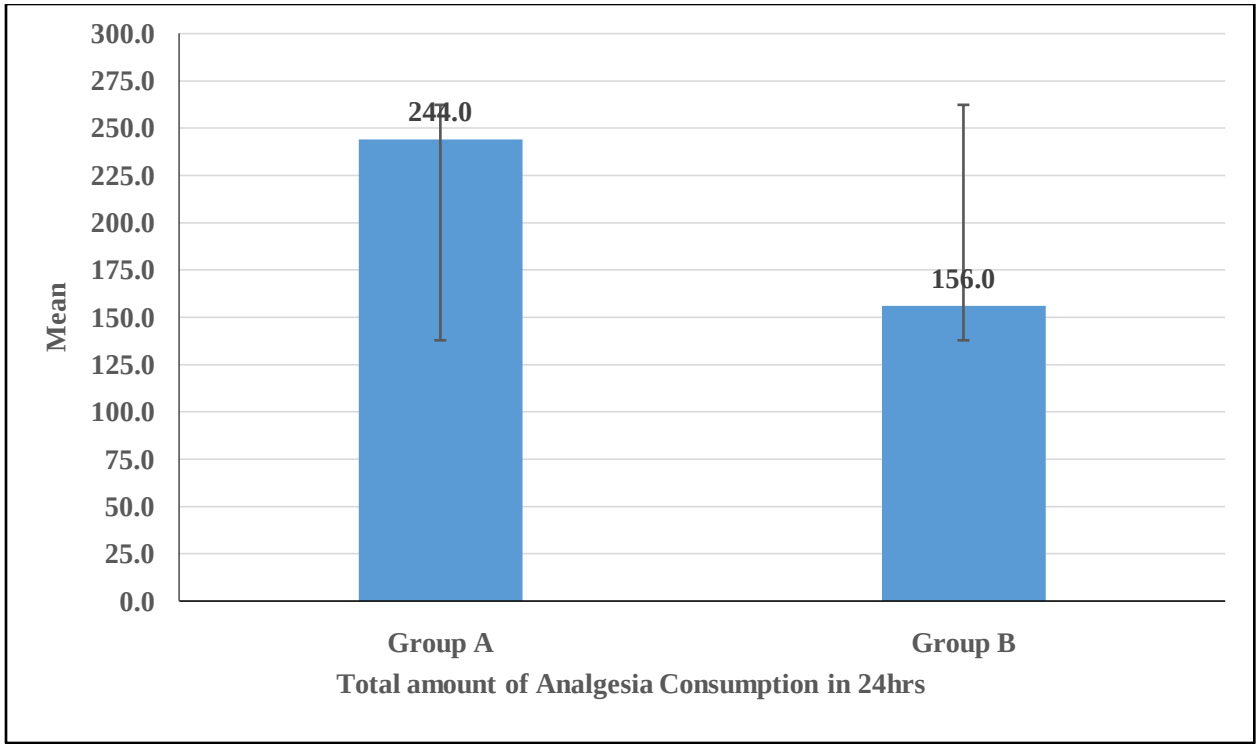

Figure 1:- Comparison of analgesic consumption in the groups in 24 hours.

In this study, we utilized NRS scores for assessment of pain (with a score of 0 indicating no pain and a score of 10 indicating worst possible pain) at recovery after the patient is fully awake from anesthesia, at the end of 1, 2, 4, 8, 12 and 24 hours by the anesthetist who is blinded to the treatment allocation. After the end of 24hours of postoperative analgesia consumption, the time to the first analgesia request is recorded. The mean value of the parameters recorded is given in Table 3. It was found that the overall mean scores in group A were higher than group B and the p values at first four hours intervals were found to be significant indicating that the pain control was better in group B as compared to group A patients.

Table 3:- Numerical Rating Scale for assessment of pain at different intervals.

	Group A	Group B	p-value
1 hour	3.08	1.96	0.001*
2 hours	3.52	2.08	0.012*
4 hours	3.6	2.96	0.017*

6 hours	3.4	2.70	0.215
8 hours	3.16	2.98	0.365
12 hours	2.9	2.88	0.451
24 hours	2.81	2.75	0.532

* Significant

Time for 1st analgesia request was seen in 60% in group A at 2nd hour and 32% in 1st hour. Time for 1st analgesia request was seen in 60% of patients in group B in 3rd hour and 20% in 2nd hour given in figure 2. The overall consumption of analgesia at the end of 24 hours was greater in Group A as compared to Group B depicted in Figure 1.

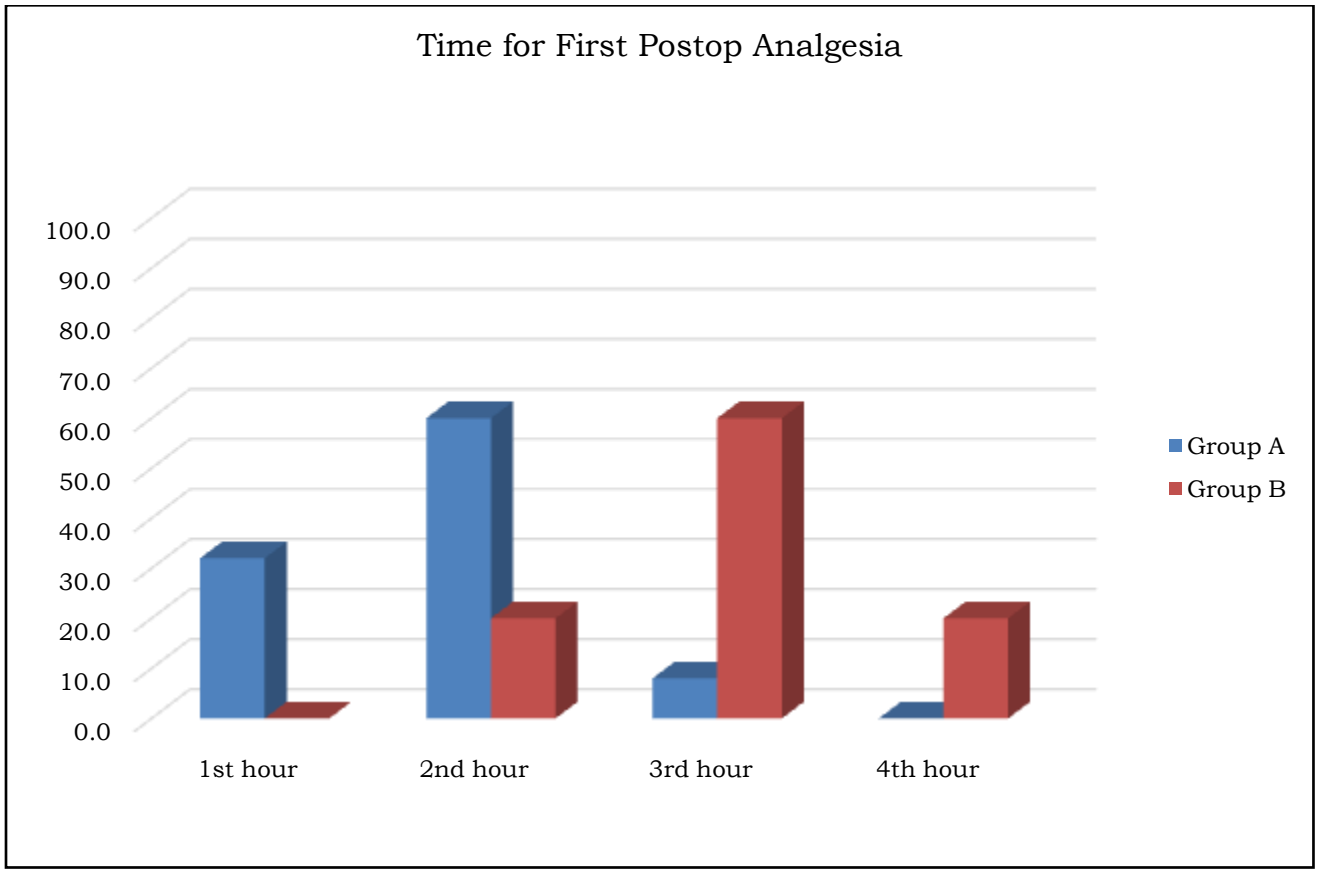

Figure 2:- Comparison of time for First analgesia request in both the groups

Discussion:-

Our study showed that the total tramadol consumption was lower in paracetamol-diclofenac group B as compared to paracetamol alone group A. In this study we found the mean tramadol consumption in group A was 244 ± 36.28 mg versus 156 ± 8.81mg consumption in group B the consumption was statistically significant in group A as compared to group B. In a similar study by Samimi et al.,[21] the mean total morphine intake during the first 24 hours was considerably lower in patients taking the combination of paracetamol and diclofenac (13.9 ± 2.7 mg) than in the diclofenac group (20.1 ± 3.6 mg), with a p-value of 0.05. Tramadol, the least potent opioid studied in our study was used to treat postoperative pain. Comparing our results to Samimi et al., [20]and using the opioid conversion factor for tramadol as morphine (0.1) the paracetamol group A consumed 24.4 mg of morphine versus 15.6 mg of morphine for group B. Montgomery et al., [22]in a similar study found the total postoperative requirement in the paracetamol plus diclofenac group was (18.5–35.8) (mean, 95% CI) it was lower than paracetamol alone group where consumption was (36.1–53.6). They concluded that the amount of post-operative morphine consumption was reduced to one-third in the combination group as compared to the paracetamol alone group in women undergoing elective abdominal gynecological procedures. The results of this study are in concordance with the results of the above study. Opioids are used for post-operative pain management. But this is associated with side effects like

dizziness, nausea,vomiting,constipation,physical dependence,addiction, etc. and the practice of epidural and opioid-free analgesia is difficult in a low-resource setting. Therefore, Multimodal analgesia is one of the approaches used for postoperative pain control in limited-resource settings. Mossa et al.,[23]have assessed the total opioid consumption between the paracetamol plus diclofenac combination and paracetamol alone group and they found significantly lower total morphine consumption in paracetamol-diclofenac combination: mean (SD) 2.9 (±1.5) mg compared to paracetamol alone 5.5 (±1.5) mg with $p < 0.01$. In a study conducted by Aweke Z et al.,[20] patients who underwent laparotomy surgeries were randomly allocated into group P (paracetamol 1gm), group PD (paracetamol 1gm+inj.diclofenac 75mg), group PT (paracetamol 1gm+inj.tramadol 100mg).NRS scale was used in this study to assess pain. The mean total tramadol was compared among three groups, and it was found to be significantly higher in group P(250 mg) compared to group PD (173mg) and group PT (154 mg).They concluded that a preemptive combination of drugs in group PT and group PD reduced total tramadol consumption and prolonged the time to 1st rescue analgesic compared to group P alone. In our study, we found the NRS scores were significantly lower in group B as compared to group A the values were significant for the first four hours between the two groups (table 3) In a study conducted by Caliskan E et al., [24] n=60 children who underwent lower abdominal surgery were randomly allocated into group 1 (paracetamol IV 15 mg/kg),group 2 (dipyrone 15 mg/kg), group 3 (placebo -isotonic saline).VAS score was used for assessing pain.Pethidine 0.25 mg/kg was used as a rescue analgesic.The mean total pethidine consumption postoperatively was compared between 3 groups and was seen significantly higher in group 1 (9.5 ± 5.9), group 2 (10 ± 3.4), and group 3(10.6 ± 4.7). Time to 1st analgesia request was seen significantly later in group 1 (2.9 ± 1.3 hr), group 2 (2.1 ± 1.3hr),and group 3 (1.8 ± 1.3). Solmaz et al., [25] found lower mean VAS scores in acetaminophen plus tramadol combination as compared to acetaminophen alone at the first and second hours (2.10 ± 1.48 Vs. 4.75 ± 3.05 p = 0.030 and 3.30 ± 1.71 Vs. 6.10 ± 1.86 0.020, respectively) and they found the difference in VAS distribution appeared similar after second hour in both groups (3.45 ± 1.63 Vs. 3.95 ± 1.43 p = 0.129). Multimodal analgesia, which combines many analgesic modalities into a single analgesic regimen, may have the best chance of preventing the neural systems from becoming too sensitive to noxious stimuli. Increased pain threshold, reduced nociceptors activation, and multi-level blockage of nociceptive inputs are all features of efficient pre-emptive analgesic treatments. [26] Our findings demonstrated that paracetamol alone was not as effective as combo treatment. The low pain scores in the combination groups may be attributed to reduced central nervous system excitability brought on by the blocking of nociceptive inputs at several sites before tissue injury.

Limitations of the current study: included lack of control for other factors which included the size of incisions used in surgery and the operative skill of the surgeon to produce minimal tissue damage. The smaller sample size is also one of the important factors. Another crucial factor was we did not include one control group with a placebo (saline) which would have provided a more accurate assessment of the analgesic effects of both groups. Therefore, the results of the study must be considered with all the limitations before generalizing the results.

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