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Araştırma

Administration of Paracetamol, Diclofenac Sodium, and Tramadol for Postoperative Analgesia After Coronary Artery Bypass Surgery

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ABSTRACT

Objective: *In this study we aimed to compare the effects of paracetamol, diclofenac sodium, and tramadol administration on postoperative pain during postoperative period of the patients who underwent coronary artery bypass grafting (CABG).*

Material and Method: *After acquirement of the approval of ethics committee and informed consent of the patients, 200 patients with normal renal and liver functions and an ejection fraction value of 40 % who would undergo CABG were included in the study. The patients were randomly divided into four groups: Group I (n=50) paracetamol group (IV); Group II (n=50) diclofenac sodium (IM) group; Group III (n=50) tramadol (IV) group, and Group IV (n=50) placebo group. Group IV patients were given only 2 µg/kg/h of fentanyl. Hemodynamic values and biochemical parameters were recorded. Postoperative pain was assessed using Visual Analog Scale (VAS).*

Results: *In the placebo group, $PaCO_2$ levels were higher, mean arterial pressure was higher and extubation time was longer than the other groups. There was no statistically significant difference between the three analgesia groups.*

Conclusion: *Based on our study results, analgesic effect of IV paracetamol appears to be similar to diclofenac and tramadol.*

Keywords: *paracetamol, diclofenac sodium, tramadol, coronary artery bypass grafting, postoperative analgesia*

ÖZ

Koroner Arter Baypas Cerrahisinden Sonra Postoperatif Analjezide Parasetamol, Diklofenak Sodyum ve Tramadol Verilmesi

Amaç: *Bu çalışmada, koroner arter baypas (KABG) ameliyatı geçiren hastalara postoperatif süreçte parasetamol, diklofenak sodyum ve tramadol uygulamasının postoperatif ağrı üzerine etkilerini karşılaştırmayı amaçladık.*

Gereç ve Yöntem: *Etik komite ve bilgilendirilmiş onamları alınan KABG uygulanacak normal böbrek ve karaciğer fonksiyonlarına sahip ve ejeksiyon fraksiyonu %40 üzerinde olan 200 hasta çalışmaya alındı. Hastalar rastgele 4 gruba ayrıldı; grup I (n=50) parasetamol IV, grup II (n=50) diklofenak sodyum IM, group III (n=50) IV tramadol alan hastalar, ve grup IV (n=50) plasebo. Grup IV'teki hastalar yalnızca 2 µg/kg/saat fentanil aldı. Hemodinamik ve biyokimyasal parametreler kaydedildi. Postoperatif ağrı vizüel analog skala (VAS) ile değerlendirildi.*

Bulgular: *Plasebo grubunda ekstübasyon zamanı daha uzun, $PaCO_2$ seviyeleri ve ortalama kan basıncı diğer gruplara göre daha yüksekti. Diğer analjezi grupları arasında istatistiksel olarak anlamlı fark yoktu.*

Sonuç: *Çalışmamızda, IV parasetamolün analjezik etkisinin diklofenak ve tramadole benzer olduğu görüldü.*

Anahtar kelimeler: *parasetamol, diklofenak sodyum, tramadol, koroner arter baypas greft, postoperatif analjezi*

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INTRODUCTION

Despite the advances in the pathophysiology and treatment of pain, access to information, and use of new drugs and complex drug administration systems, treatments are still inadequate to relieve postoperative pain in many patients. Studies conducted in this area

revealed that 30 to 75 % of postoperative patients suffer from moderate or severe pain [1]. Postoperative pain is an acute pain starting with surgical trauma and gradually decreasing with tissue healing. Pain has a significant role in the formation of a stress response induced by the surgery [2].

Consistent with the literature data, proper and adequate postoperative pain management is an important factor in increasing the patient comfort, speeding up the postoperative recovery and healing process, shortening the length of hospital stay and reducing treatment costs [3]. It has been clearly shown that the morbidity and mortality rates of a surgery can be reduced, and early recovery after cardiac surgery can be ensured by relieving the postoperative pain. In the treatment of postoperative pain, it is possible to prevent almost all complications when the appropriate method is selected by considering the risks of the method and physical condition of the patient, severity of the pain, expected duration of severe pain, location and quality of the surgical intervention, staff and technical possibilities.

Recently, three drug groups are used as well as other methods in postoperative pain management. These include opioids, non-opioids, and local anesthetic drugs administered using regional techniques [4,5]. In the present study, we aimed to compare the postoperative analgesic efficacy, and hemodynamic effects of paracetamol, diclofenac sodium, and tramadol hydrochloride after coronary artery bypass grafting (CABG).

MATERIAL and METHODS

This prospective, double-blind, randomized-controlled study was conducted at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center, after receiving the approval of the institutional Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with Declaration of Helsinki the statement of ethical principles for medical research involving human subjects. A total of 200 patients who underwent CABG with normal renal and liver functions with an ejection fraction value of 40% were included. None of the patients had diabetes or peptic ulcer history. All patients were randomly divided into four groups: Group I (n=50) IV paracetamol group (Perfalgan flacon 100 mL, 10 mg/mL, Bristol Myers Squibb), Group II (n=50) IM diclofenac sodium group (Dikloron 75 mg, Deva), Group III (n=50) IV tramadol group (Contramal 100 mg, Abdi İbrahim), and Group IV (n=50) placebo group. In the postoperative unit, fentanyl infusion at a 2 μg/kg/h dose was given for 2 hours to provide hemodynamic stability. Thirty minutes before the patients were extubated, Group I received analgesic treatment with paracetamol IV at 15 min and every 6 h (average total dose 4 g), Group II, 75 mg IM diclofenac sodium at every 6 h, and Group III , 5 mg/h IV tramadol infusion after a 50 mg of loading dose. Group IV was given only 2 μg/kg/h of fentanyl for 2 hours. Hemodynamic variables such as heart rate (HR), arterial blood pressure (BP), and arterial blood gas were recorded at prespecified time points. Complete blood count, fasting blood sugar, urea, creatinine, albumin, aspartate transaminase (AST), and alanine transaminase (ALT) levels were also analyzed. Postoperative pain was assessed using the Visual Analog Scale (VAS). Extubation time and postoperative length of stay in intensive care unit (ICU) among patients were recorded. Prespecified time points were as follows: T0: postoperative 1st h, T1: postoperative 6th h, T2: postoperative 12th h, and T3: postoperative 24th hour.

Statistical analysis was performed using the SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean (± standard deviation (SD) and percentages. One-way analysis of variance (ANOVA) was used to compare quantitative data, while the chi-square test was used to compare qualitative data. The Tukey HDS test was used to identify the group which caused the difference. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Of a total of 200 patients, 168 (84%) were males and 32 (16%) were females. The mean age was 55.67±9.73 (range: 27 to 80) years. There was no statistically significant difference among the groups in terms of age and sex distribution ($p>0.05$). Demographic characteristics of the patients and baseline laboratory test results are shown in Tables 1, and 2, respectively.

Table 1. Demographic characteristics.

Variable Mean±SD	Group I (n=50) Paracetamol	Group II (n=50) Diclofenac	Group III (n=50) Tramadol	Group IV (n=50) Placebo	P
Age (year)+	57.54±9.44	55.82±9.56	53.60±10.31	55.74±9.46	0.249
BSA (m^2)+	1.90±0.15	1.88±0.18	1.89±0.13	1.88±0.17	0.888
Sex, n (%)++					
Female	7 (14.0%)	8 (16.0%)	8 (16.0%)	9 (18.0%)	0.960
Male	43 (86.0%)	42 (84.0%)	42 (84.0%)	41 (82.0%)	0.960

*+One-way ANOVA; ++Chi-square test, *p<0,05*

Table 2. Baseline biochemical parameters.

Variable	Mean±SD	Reference
Urea (g/day)	14.59±2.98	8.6-24
AST (U/L)	20.74±5.40	10-37
ALT (U/L)	20.76±8.37	9-50
Albumin (g/dL)	4.34±0.28	3.7-5.4
Creatinine (mg/dl)	1.04±0.13	0.7-1.2

ALT, aspartate aminotransferase; ALT, alanine aminotransferase

The VAS scores of the placebo group at 12th h were statistically significantly higher than the other groups (p<0.01). In addition, the VAS scores of the paracetamol group at 12th h were statistically significantly lower than the VAS scores of the diclofenac sodium and tramadol groups (p<0.01). However, there was no statistically significant difference in the VAS scores of the diclofenac sodium and tramadol groups at 12th h (Figure, Table 3).

There was no statistically significant difference in the extubation times among the groups, except the placebo group. Extubation times of the patients in the placebo group were statistically significantly higher than the other groups. Extubation times of the patients in the paracetamol group were statistically significantly lower when compared with the diclofenac sodium group (p<0.01). In addition, there was no statistically significant difference in the mean postoperative length of stay in ICU among the three analgesia groups (p>0.01), but the placebo group had longer postoperative length of stay in ICU

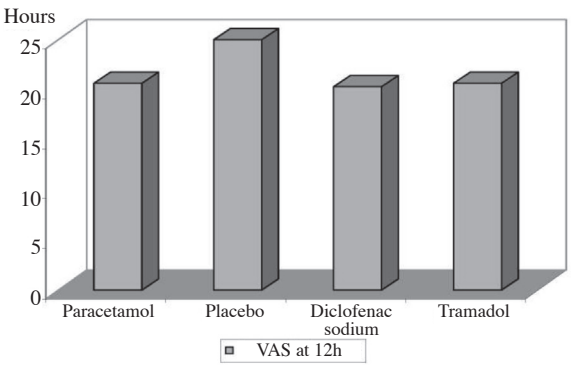

Figure. VAS scores.

There was a statistically significant difference in the nausea/vomiting rates among the groups (p<0.01). The incidence of nausea/vomiting in patients in the tramadol group (40%) was statistically significantly higher than the other groups (p<0.01). However, there was no statistically significant difference in the incidence of nausea/vomiting among the paracetamol, diclofenac sodium and placebo groups (p>0.05) (Table 3). $PaCO_2$ measurements at baseline, 1st, 6th,

Table 3. Patient parameters.

	Group I (n=50) Paracetamol	Group II (n=50) Diclofenac	Group III (n=50) Tramadol	Group IV (n=50) Placebo	P
12th h VAS+	0.42±0.64	1.70±0.76	1.78±0.71	6.10±1.69	*0.01***
Extubation time(h)+	8.72±2.72	7.53±1.77	8.51±2.07	10.45±1.17	*0.01***
Postoperative ICU length of stay (h)+	20.63±1.92	20.31±1.65	20.61±0.92	24.99±0.53	*0.03*
Nausea/Vomiting ++	n (%)	n (%)	n (%)	n (%)	
Yes	0 (0.0%)	3 (6,0%)	20 (40.0%)	5 (10.0%)	***0.01****
No	50 (1000.0%)	47 (94,0%)	30 (60.0%)	45 (90.0%)	

*+Oneway ANOVA Test, ++Chi-square test, ** p<0.01*

Table 4. $PaCO_2$ measurements according to study groups.

$PaCO_2$ (mmHg) Mean±SD	Group I (n=50) Paracetamol	Group II (n=50) Diclofenac	Group III (n=50) Tramadol	Group IV (n=50) Placebo	P
Baseline	33.35±4.50	32.56±5.07	33.78±4.66	32.71±1.76	0.06
1st h	34.39±3.16	32.58±4.45	34.03±4.62	33.35±1.57	0.07
6th h	33.05±3.10	32.70±3.62	36.59±4.78	34.79±2.18	0.001*
12th h	32.23±2.23	31.93±2.49	36.21±4.92	37.78±1.47	0.001*

**p<0.01, $PaCO_2$, partial pressure of carbon dioxide.*

Table 5. PO_2 measurements according to study groups.

$PaCO_2$ (mmHg) Mean±SD	Group I (n=50) Paracetamol	Group II (n=50) Diclofenac	Group III (n=50) Tramadol	Group IV (n=50) Placebo	P
Baseline	220.02±99.42	239.07±82.61	244.48±57.30	232.52±49.35	0.03
1st h	167.37±52.28	150.72±26.75	145.02±18.61	132.44±42.64	0.03
6th h	151.37±32.55	142.03±22.83	135.21±34.23	130.88±11.93	0.03
12th h	128.44±28.98	132.35±23.37	131.63±17.35	129.44±10.84	0.03

p<0.01. PO_2, partial pressure of oxygen.

Table 6. MAP measurements according to study groups.

MAP (mmHg) Mean±SD	Group I (n=50) Paracetamol	Group II (n=50) Diclofenac	Group III (n=50) Tramadol	Group IV (n=50) Placebo	P
Baseline	94.38±13.25	93.30±14.53	97.52±13.68	94.46±5.70	0.06
1st h	85.96±15.49	84.34±7.16	88.44±11.47	90.96±10.14	0.025*
6th h	84.20±14.34	85.40±9.43	86.28±8.76	95.34±6.93	0.001**
12th h	80.40±7.80	82.18±8.81	83.76±11.20	105.58±7.06	0.001**

p<0.01. PO_2, partial pressure of oxygen.

and 12th h are shown in Table 4. We found no statistically significant difference in the baseline $PaCO_2$ levels among the groups (p>0.01). However, the patients in the tramadol and placebo groups had statistically significantly higher $PaCO_2$ levels compared to paracetamol and diclofenac sodium groups (p<0.01). PO2 measurements at baseline, 1st, 6th, and 12th h are shown in Table 5. There was no statistically significant difference in the baseline PO_2 levels among the groups (p>0.05). In addition, there was no statistically significant difference in the baseline and 1st h mean arterial pressure (MAP) levels among the groups (p>0.01) (Table 6). There was statistically significant difference in the baseline and 1st mean arterial pressure (MAP) levels among the groups The 6th, and 12th h MAP levels of the patients in the tramadol and placebo groups were statistically significantly higher compared to diclofenac and paracetamol groups (p<0.05, p<0.01). Blood glucose was also higher in the placebo group, but there was no significant difference in the glucose levels among all groups.

DISCUSSION

Pain management in the postoperative care setting is of utmost importance for patients who underwent CABG. Therefore, pharmacological and interventional approaches have been developed for postoperative analgesia. Currently, there is an increase in the mean age of the patients, and in the number of comorbidities in patients undergoing CABG. Overall, a method of postoperative analgesia which is cost-effective and comfortable for the patient with minimum complication rates and side effects which also shortens the duration of postoperative stay should be chosen. Tachycardia and hypertension induced by pain are frequently seen during the postoperative period , and the administration of high dose fentanyl and other opioids may prolong respiratory center depression. Hemodynamic stability can only be obtained through a good analgesia management in this period where myocardial oxygen consumption in cardiac patients is critical [3]. Therefore, early extubation can be

performed by shortening the duration of mechanical ventilation support [6].

In our study, all groups received fentanyl infusion (2 μg/kg/h) for 2 hours to ensure hemodynamic stability during the postoperative period. The placebo group did not receive any additional analgesic drug after extubation. VAS scores, extubation time, postoperative length of stay in ICU, $PaCO_2$, MAP, glucose levels in the placebo group were higher, compared to the patients who received analgesia during the postoperative period. Attempts at maintenance of hemodynamic stability, despite 2-h fentanyl administration (2 μg/kg/h) for hemodynamic stability during the postoperative period, suggests that postoperative analgesia is required to shorten the extubation time and the length of stay in the postoperative ICU period. However, drugs used as postoperative analgesics following the hemodynamic stability after CABG have several risks. Opioid use is associated with the risk of respiratory depression and sedation, tramadol with the risk of respiratory depression, sedation, nausea/vomiting, and non-steroidal anti-inflammatory drugs (NSAIDs) with the risk of bleeding diathesis, increased bleeding, and consequently recurrent bleeding. Therefore extubation time, and postoperative length of stay in ICU are prolonged. The postoperative analgesic drug to be used for this purpose is desired to be able to relieve the pain effectively, with minimum side effects, and easy applicability.

Combination of analgesics from different pharmacological classes relieves the postoperative pain, whereas minimizing the side effects of each medication is a commonly used strategy [9]. This concept of "balanced analgesia", which is also referred to as multidrug analgesia, can be applied in combination with opioids and non-opioids (i.e., NSAIDs, paracetamol) [2]. Opioid analgesics reflect a standard approach in the postoperative pain management. However, respiratory depression, sedation, and nausea/vomiting are the main reasons why they are not often preferred. The cumulative opioid dose is required to be reduced to decrease its possible side effects. Low-dose opioid use through balanced analgesia may improve respiratory functions, and reduce nausea, vomiting and sedation [9,10].

In our study, "balanced analgesia" method was performed. Fentanyl was given as 2 μg/kg/h for the first 2 h to provide hemodynamic stability. Then, it was maintained with non-opioid (NSAID, diclofenac, and paracetamol) and opioid tramadol administration . High doses of opioids are not commonly used, as they have adverse effects on respiratory functions, and cause delayed arousal due to sedation [1,5,9]. In a comparative study by Coetze et al. [11], concerning use of postoperative tramadol and morphine cognitive functions were assessed by p-deletion test, and all patients in the tramadol group were observed to be not able to complete the p-deletion test at the first 15 min, and 50% of the patients could not complete the test at the end of 30 minutes. These results are consistent with our study results, indicating that these side effects are more prevalent, compared to NSAIDs, although tramadol does not cause as much respiratory depression and sedation as opioids.

Increase in bleeding tendency is one of the main complications expected with the use of NSAIDs [12]. Therefore, use of NSAIDs as postoperative analgesics after CABG is not recommended. In the present study, we excluded patients who had the risk of peptic ulcer and bleeding, since these drugs should be used with caution in such patients. One of the most common side effects of tramadol, which is an opioid-like drug, is nausea/vomiting. This side effect of tramadol was also observed in our study population. However, its frequency was lower in the diclofenac and placebo groups, while none of the patients in the paracetamol group experienced this side effect. In addition, postoperative nausea and vomiting were also associated with residual effects of anesthetic gases and surgical procedures. In their study, Avellaneda et al. [13] compared the effects of IV metamizole 2 g, ketorolac 30 mg, and paracetamol 500 mg on hemodynamic variables in acute postoperative pain after cardiac surgery and pain control. The authors found an analgesic effect at 60th min with all study medications. None of the drugs caused clinically significant hemodynamic instability. In our study, we treated hemodynamically stable patients with IV paracetamol, IV tramadol, and IM diclofenac, and could not find any significant hemodynamic instability.

In conclusion, the agent to be used for the management of postoperative pain after CABG is desired to relieve the pain effectively with advantages of easy

applicability, and minimum side effects. Based on our study results, the effect of IV paracetamol on such pain appears to be similar to diclofenac and tramadol with lower side effects. However, further, large-scale and well-designed studies are required to confirm our findings.

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