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Ondansetron in the Prevention of Post Cardiotomy Delirium after Coronary Artery Bypass Grafting Surgery

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ABSTRACT

Objective: To determine the efficacy of Ondansetron as a prophylctic agent in patients undergoing Coronary Artery Bypass Grafting.

Study Design: Quasi-experimental study.

Place and Duration of study: Adult Cardiac Surgery Department, AFIC/NIHD Rawalpindi Pakistan, from Nov 2022 to Feb 2023.

Methodology: A total of 156 patients undergoing Coronary Artery Bypass Grafting Surgery irrespective of age and gender were included in the study via nonprobability consecutive sampling. Patients who had a previous history of psychiatric illness, and those in whom delirium could not be reliably tested were excluded from the study. The study population was divided into two groups (group A and group B). Those in the group A received 8mg Ondansetron intravenously on zero, first and second post-operative day. Group B did not receive any intervention. Descriptive statistics were used to measure percentages, frequencies and Mean±SD. Comparison between variables was made by Chi-square test for categorical variables and t-test for continuous variables. $p<0.05$ was considered statistically significant.

Results: Total 156 patients were included in the study and mean age of the patients was 59.47±10.98 years. A total of 3(14.3%) patients who had been given Ondansetron compared to 18(85.7%) patients who were not given Ondansetron developed delirium ($p<0.001$). Other factors significantly associated with post cardiotomy delirium were age ($p<0.001$), hypertension ($p<0.001$), and diabetes ($p=0.03$).

Conclusion: Our study revealed that Ondansetron can be used effectively to reduce the incidence of post cardiotomy delirium in patients of coronary artery bypass grafting.

Keywords: Coronary artery bypass grafting, Ondansetron, Post cardiotomy delirium, Serotonin.

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INTRODUCTION

Post Cardiotomy Delirium (PCD) is a major morbidity following cardiac surgery with a quoted incidence of 8.4-67%.[1,2] It is defined as an acute change in behavior or mental status of the patient and has a variety of clinical manifestations. Patients may present with hyperactive delirium and display agitated, irritated behavior or they may present with disorientation, confusion, memory loss, lethargy or hallucinations. It is more common in 'open heart' procedures such as valvular surgery as compared to 'closed heart' surgeries such as Coronary Artery Bypass Grafting (CABG).[3] Hypoactive delirium is the most common form of PCD.[4] Numerous risk factors have been highlighted including older age, use of narcotics and alcohol, preoperative organic brain disease such as prior stroke, parkinsonism or other forms of dementia, severe cardiac disease or emergency surgery and complex surgery with prolonged cardiopulmonary bypass time.[5]

PCD significantly correlates with a prolonged hospital stay, reduced cognitive and functional recovery, considerable distress to family members and increased morbidity and mortality.[6] Important morbidities associated with PCD include postoperative respiratory insufficiency and significantly higher incidence of sternal instability likely to require surgical revision of the sternal wound.[7]

The exact pathophysiology of PCD is not known but it is suggested that neural inflammation associated with the systemic inflammatory state, endothelial dysfunction and hormonal imbalance induced by Cardiopulmonary Bypass (CPB) and embolic phenomenon resulting from handling of the aorta maybe underlying mechanisms.[4] The serotonergic system is linked with anxiety and depressive disorders, and studies have suggested that it may play an important role in acute delirium.[8] Altered serotonin activity

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associated with CPB may also be one of the possible mechanisms which could account for the high rates of delirium in post cardiotomy patients.

Ondansetron, a 5-HT3-receptor antagonist, is a drug commonly used for control of postoperative nausea and vomiting and has few significant adverse effects.[9,10] Studies have shown that Ondansetron may be useful in treating patients who have been diagnosed with PCD in the intensive care setting.[11] Considering the dearth of data regarding Ondansetron as a prophylactic agent for the complication, especially in our region, we aimed to reduce this gap. The purpose of the present study was to evaluate the effectiveness of Ondansetron as a prophylactic agent in prevention of PCD.

METHODOLOGY

After taking ethical approval from the Institutional Ethical Review Board (IERB) (letter#9/2/R&D/2022/215) the Quasi-experimental study with non-randomized selection of study population was carried out from November 2022 to February 2023 at the Department of Cardiac Surgery, Armed Forces Institute of Cardiology.

Sample size of 126 was calculated taking prevalence of PCD as 9%,95% confidence interval and 5% margin of error using the WHO calculator.[12] However, data was collected from 156 patients.

Inclusion Criteria: All patients undergoing CABG surgery irrespective of age and gender were included in the study.

Exclusion Criteria: Patients who had a previous history of psychiatric illness, and those in whom delirium could not be reliably tested (e.g., previous debilitating stroke, cerebral palsy, previous history of dementia, recent history of a psychotic disorder, severe hearing disability, inability to understand) were excluded from the study.

After taking prior written consent, 156 patients meeting the eligibility criteria were enrolled via a non-probability consecutive sampling technique. The study population was divided into two groups (group A and group B). Those in the group A received 8mg Ondansetron intravenously on zero, first and second post-operative day. Group B did not receive any intervention. The Confusion Assessment Method (CAM-ICU) tool was used once daily to assess which patients amongst both groups developed delirium. Patients were followed up until the day of discharge.

Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 28:00. Descriptive statistics were used to measure percentages, frequencies and Mean±SD. Comparison between variables was made by Chi-square test for categorical and t-test for continuous variables. $p \leq 0.05$ was considered statistically significant.

RESULTS

In this study, 156 patients were divided into two groups (A and B). 69(44.2%) patients in group A received Ondansetron whilst the 87 (55.7%) patients in group B did not receive Ondansetron. The mean age was 59.47±10.98 years with a range from 27-76 years. There were 120(76.9 %) males in the study population whilst there were 36(23.1%) females (Table-I).

Table-I: Demographic and Pre-operative Parameters of study groups (n=156)

Variables		Group A (n=69)	Group B (n=87)
		Frequency (%)	Frequency (%)
Age(years) (Mean±SD)		60.16±10.25	58.79±9.46
Height (cm) (Mean±SD)		166.01±7.93	167.31±9.91
Weight (kg) (Mean±SD)		73.80±14.78	78.29±13.19
Gender	Female	21(30.4)	15(17.2)
	Male	48(69.6)	72(82.8)
Smoking status	Active	9(13.0)	36(41.4)
	Ex Smoker	18(26.1)	0(0)
	Non-Smoker	42(60.9)	51(58.6)
Hypertension	No	18(26.1)	24(27.6)
	Yes	51(73.9)	63(72.4)
Diabetes	No	36(52.2)	39(44.8)
	Yes	33(47.8)	48(55.2)
Ejection Fraction(%)	Severe Dysfunction (<30)	3(4.3)	0(0)
	Moderate Dysfunction (30-39)	3(4.3)	9(10.3)
	Mild Dysfunction (40-49)	21(30.4)	33(37.9)
	Normal (50-70)	42(60.9)	45(51.7)

54(34.6%) out of the 156 patients had off-pump coronary artery bypass grafting. For those who underwent conventional CABG, mean cross clamp time was 75.36±37.26 mins in group A while it was 66.32±31.73 mins in group B. Mean CPB time was 123.26±49.46 mins in group A while it was 106.77±50.80 mins in group B (Table-II).

Table-II: Intra-operative parameters of study groups (n=156)

		Mean±SD Frequency(%)	Mean±SD Frequency(%)
Variables		Group A	Group B
Cross Clamp Time (mins) (Mean±SD)		75.36±37.26	66.32±31.73
Total Bypass Time (mins) (Mean±SD)		123.26±49.46	106.77±50.80
Number of grafts	1-2	24(34.8)	21(24.1)
	3-4	45(65.2)	66(75.9)

The results of the study showed that PCD was not significantly associated with CABG (p=0.06), but was found significantly associated in diabetic (p=0.03) and hypertensive patients (p-value<0.001). There was no significant difference in development of PCD between gender and smoking status (Table-III).

Table-III: Comparison of Post Cardiotomy Delirium with Demographics and Pre-operative Parameters (n=156)

Variables		Post Cardiotomy Delirium		p-value
		No (n=135) Frequency (%)	Yes (n=21) Frequency (%)	
Gender	Female	30(22.2)	6(28.6)	0.71
	Male	105(77.8)	15(71.4)	
Smoking status	Active	36(26.7)	9(42.9)	0.10
	Ex-Smoker	18(13.3)	0(0)	
	Non-Smoker	81(60)	12(57.1)	
Hypertension	No	27(20)	15(71.45)	<.001
	Yes	108(80)	6(28.6)	
Diabetes	No	60(44.4)	15(71.4)	0.03
	Yes	75(55.6)	6(28.6)	
Type of *CABG	Conventional	84(62.2)	18(85.7)	0.06
	Off-pump	51(37.8)	3(14.3)	
Ejection Fraction	Severe Dysfunction	3(2.2)	-	0.12
	Moderate Dysfunction	9(6.7)	3(14.3)	
	Mild Dysfunction	51(37.8)	3(14.3)	
	Normal Ejection Fraction	72(53.3)	15(71.4)	

CABG = Coronary Artery Bypass Grafting

The patients who received Ondansetron had significantly decreased incidence of post-cardiotomy delirium (p=0.006) as compared to those who did not receive Ondansetron (Table-IV).

Results also showed that the development of PCD likely increases with age (p-value<0.001). Total bypass time, and cross-clamp time did not have a significant mean difference between study groups p>0.05 (Table-V).

Table-IV: Comparison of post cardiotomy delirium with Ondansetron (n=156)

		Post cardiotomy delirium		p-value
		No (n=135) Frequency (%)	Yes (n=21) Frequency (%)	
Ondansetron	Group A	66(48.9)	3(14.3)	0.006
	Group B	69(51.1)	18(85.7)	

Table-V: Comparison of Post Cardiotomy Delirium with Per-operative Parameters (n=156)

Variables	Post Cardiotomy Delirium	Mean±SD	p-value
Cross-Clamp Time (mins)	No	70.46±34.79	0.78
	Yes	68.06±32.35	
Total Bypass Time (mins)	No	116.98±51.57	0.11
	Yes	97.61±44.05	
Age (years)	No	58.55±9.98	<.001
	Yes	64.86±6.43	

DISCUSSION

PCD is a major morbidity amongst patients undergoing CABG surgery. It not only increases hospital stay, but results in increased incidence of sternal instability, wound infection, respiratory complications, family distress and an increased mortality.[13] Our study reinforces the fact that PCD is multifactorial and proper identification of risk factors prior to surgery can help physicians adopt precautions which can decrease its incidence.

In this study, diabetics (p=0.03) and hypertensive patients (p<0.001) had a higher incidence of delirium and this is supported by numerous studies.[14-15] Both HTN and diabetes accelerate the atherosclerotic process, particularly in the aorta and the carotid arteries, and manipulation during surgery can lead to embolic showering leading to PCD.[16] Cerebrovascular disease is also strongly associated with both of these ailments, and can be another cause for the increased rates of neurocognitive defects. It is plausible that metabolic changes accompanied by both diabetes and hypertension puts patients at risk for PCD.

Advanced age is associated with microvascular cerebral changes and an increased atherosclerotic burden. This, coupled with the impaired elimination of anesthetic agents and drugs, may account for the higher incidence of delirium with advanced age. Numerous studies have shown similar outcomes when comparing age with PCD.[5, 15,17-18]

CPB time (68.06±32.35; p=0.78) and CX time (97.61±44.05; p=0.11) were not notably increased in those who developed delirium in our study. Whilst some previous studies have shown that increased CBP

and cross-clamp time lead to increased incidence of PCD,[17,19,20] other studies have shown that they are not.[2,5,14] This disparity might be due to the differences in perfusion protocols and techniques of grafting being used in various centers.

Several studies have investigated the incidence of PCD in patients undergoing off-pump CABG compared to those undergoing conventional CABG. Some studies have suggested that off-pump CABG may be associated with a lower incidence of PCD compared to on-pump CABG.[1,21-22] Similar results were shown in our study where 3 (14.3%) off-pump CABG vs on-pump CABG 18 (85.7%) also showed reduction in the incidence of PCD. The increase in neurocognitive complication associated with conventional CABG are postulated to be due to perfusion abnormalities,[23] and increased exposure to inflammatory mediators as a result from cardiopulmonary bypass.[24] In the present study however, neither the type of CABG (conventional vs off-pump) nor factors related to only conventional CABG such as cross clamp time and total bypass time were significantly associated with PCD raising the possibility that these factors might not be as pertinent as previously thought (p>0.05).

The results of our study showed that the administration of Ondansetron to post CABG patients results in significantly decreased incidence of PCD 3 (14.3%), p=0.006. Previous studies have shown its efficacy in treating PCD,[24-25] but there is a paucity of data studying Ondansetron as a prophylactic agent in its prevention. Serotonin has been strongly associated with anxiety, and serotonin levels are found to be raised in delirious patients.[25] The serotoninergic system, along with many other systems, is affected by CPB and Sharif A Sabe *et al*. showed in 2018 an altered response to serotonin in patients exposed to cardiopulmonary bypass.[26] Therefore it can be hypothesized that impaired activity of the serotonergic system might play a crucial role in development of delirium post CABG, and Ondansetron, a 5-HT3-receptor antagonist, can be used as a pharmacological agent to reduce its frequency.

LIMITATIONS OF STUDY

The study was conducted in a single center and the sample size was small. Another limitation could be that the surgeries were performed by different specialists and the surgical methods and skills may have been different in each case. Further randomized control trials should be conducted to help evaluate its effectiveness before routine use of this drug can be recommended in the post cardiac surgery ITC.

CONCLUSION

Ondansetron, which is a relatively safe drug with few adverse effects, can significantly reduce the incidence of PCD in patients undergoing CABG surgery. Prophylactic use of this drug in patients who are at high risk for development of delirium can help reduce post operative morbidity and decrease mortality.

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Conflict of Interest: None:

Authors' Contributions

Following authors have made substantial contributions to the manuscript:

DAK, MAI & SS: Manuscript writing, study concept, intellectual contribution, review of article, approval of the final version to be published.

AN, NA & RM: Study concept, approval of the final version to be published.

FUR & AS: Data collection, Review of article, Data analysis, proof reading, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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