e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(9); 727-733

Original Research Article

An Observation Study to Assess Effect of Hypoglycaemia on Platelet Indices and its Association with Occurrence of Cardio-Cerebrovascular Events in Diabetics

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Received: 28-06-2023 / Revised: 25-07-2023 / Accepted: 29-08-2023
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Conflict of interest: Nil

Abstract:

Introduction: Hypoglycaemia is the most important side effect of diabetic treatment. Hypoglycaemia should be assessed in the context of possible long-term risk of cardio-cerebrovascular complications in co-relation with platelet indices.

Method and Material: 50 diabetic patients presenting to hospital with plasma glucose <70 mg/dl requiring hospitalization for correction of hypoglycaemia were taken in study group. Sample of 50 diabetics with good glycaemic control were taken as control after matching with sex, age and other co-morbid condition for comparison. The blood sample of the patient were taken on arrival [0 hours] and 48 hours for various parameters and complete blood count including the platelet indices (MPV and PDW). All patients were followed up for the period of 3 months to note any cardio-cerebrovascular events.

Results: Majority of patients were female (60%) and mean age was 64.4 ± 12.433 years. In study group both mean of MPV and mean of PDW at the time of admission and 48 hours of admission were significantly higher than control group. On follow up we found that 13(26%) study group patients had developed cardiocerebrovascular events.

Discussion: We found that diabetics experiencing severe hypoglycaemia have higher value of platelet indices i.e. they have larger platelet volume and are probably more active metabolically. Therefore, larger platelets are more prone to develop cardio-cerebrovascular events in near future as compared to diabetics with good glycaemic control. So, the platelet indices are important, simple, cost-effective and useful in predicting the development of a cardio-cerebrovascular event sometimes in the near future.

Keywords: Hypoglycaemia, platelet indices, Cardio-cerebrovascular events.

Introduction

Diabetes mellitus is the most common metabolic disorder in the world. Hypoglycaemia is known to be intrinsic to the treatment of diabetes. Hypoglycaemia should be assessed in the context of possible long-term risk of cardio-cerebrovascular complications. Hypoglycaemia results in platelet hyperaggregability [1] and an increase in several factors involved in the coagulation cascade. Activated partial thromboplastin time is shortened, fibrinogen and factor VIII increase, and platelet counts fall in association with hypoglycemia.[2] Hypoglycaemia induces pro-inflammatory changes as increase in the plasma concentration of interleukin (IL)-6 3 and other pro-inflammatory mediators.5 Studies had confirmed the presence of an anti-inflammatory effect of insulin during infusions when euglycaemia was maintained 4 whereas hypoglycaemia exerts pro-inflammatory effects like those of hyperglycaemia and glucose intake.[5,6]

In one study involving diabetic patients with coronary heart disease who were continuously monitored for blood glucose concentrations and electrocardiographic changes, it was demonstrated that there was chest pain associated with hypoglycaemia in 20% of the patients, of whom 40% had concomitant electrocardiogram(ECG) changes consistent with ischaemia.[7] Further studies are necessary to increase our understanding of the pathophysiology of hypoglycaemia and its relationship with inflammation, platelet aggregation, and thrombotic mechanisms.

Among platelet indices, quantitative index is platelet count. Qualitative index is Mean platelet volume (MPV) that measures the activity and function of platelets. Other indices include Platelet distribution width. In certain pathological condition like acute ischaemic stroke the megakaryocyte platelet haemostatic axis is altered leading to formation of hyper functional platelets that leads to thrombosis causing acute ischaemic stroke. Increased platelet reactivity as well as shortened bleeding time, is associated with increased platelet volume. Platelets also plays important role in progression of atherosclerosis. Alpha granules and dense granules of platelet contains many chemokines, cytokines and growth factors. Release of these factors along with interaction with endothelial cells and leucocytes promotes inflammation and atherosclerosis. [8] A causal role of platelet hyperreactivity or local platelet activation in an acute coronary event has been suggested. The MPV can reflect changes in the level of platelet stimulation and by this it indirectly measures the platelet activation. It is important to find a platelet-indices that is relevant to the risk stratification of patients with ischaemic heart disease to treat them in priority for better outcome. Platelet distribution width (PDW) is an indicator of volume variability in platelets size and is increased in presence of platelet anisocytosis. PDW directly measures variability in platelet size, changes with platelet activation, and reflects the heterogeneity in platelet morphology. Under physiological conditions, there is a direct relationship between MPV and PDW. Amongst the platelet volume indices all the variable like MPV and PDW were found to have increased in IHD when compared to healthy subjects. Studies by Cameron et al, Martin et al, Martin et al, Pizzulli et al, MP Ranjith et al, Prem shankerpipliwal et al, G. Ranjani et al, and Vitthal Khode compared MPV between IHD patients and control groups and found that MPV was significantly higher in test groups as compared to control groups.[9-18] In a study by MP Ranjith et al, PDW of 60 patients with ACS was compared with 60 non-cardiac chest pain patients, and observed that PDW in ACS (14.63±0.64fl) was significantly higher than non-cardiac chest pain patients (12.01±0.55fl).[11] Mayda et al studies 692 patients with ischemic stroke and observed MPV and platelet count were independent risk factors for ischemic stroke (p=.0007, odds ratio = 0.866, 95% confidence interval).[19] Since several studies had shown increased cardio-cerebrovascular events after episode of severe hypoglycaemia, but these studies had not demonstrate anything about the effect of hypoglycaemia on platelet indices and how the hypoglycaemia exactly increases the cardio-cerebrovascular events. So, we had planned this observational study to assess effect of hypoglycaemia on with platelet indices and its association with occurrence of cardio-cerebrovascular events in diabetics.

Methods and Materials

The hospital based observational study was conducted in Department of Medicine at Dr. S. N. Medical College Jodhpur.

Source of Data

It included patients admitted in Dept. of Medicine at Dr. S. N. Medical College, Jodhpur with severe hypoglycaemia (Diabetic patients presenting to hospital with plasma glucose <70 mg/dl requiring hospitalization for correction of hypoglycaemia) in 2020 after applying the inclusion and exclusion criteria. Informed consent was taken from every case and control prior to their participation in this study. Permission from local ethical committee was taken before starting this study.

Inclusion Criteria

1. All Diabetic patients presenting to hospital with plasma glucose <70 mg/dl requiring hospitalization for correction of hypoglycaemia.
2. Patients more than 18 years of age.

Exclusion Criteria

1. Patients with bleeding diathesis, major operations or significant trauma in the past two weeks.
2. Patients with malignancy and myeloproliferative disorders.

Method of Study

Patients admitted with hypoglycaemia (Diabetic patients presenting to hospital with plasma glucose <70 mg/dl requiring hospitalization for correction of hypoglycaemia) were enquired and data regarding name, age, sex, address, religion and mobile number were recorded. Further presenting complaints like confusion, sweating, drowsiness, altered sensorium and seizures with its time and duration were noted at the time of admission. We noted any recurrence of hypoglycaemia during observation period. Patient's history regarding hypoglycaemia, hypertension, diabetes, thyroid disorder, chronic liver disease and ischemic heart disease in the past was recorded. Patients drug history whether he or she was on any insulin, OHA, anti-ischemic and anti-hypertensive drugs were asked and marked on the Performa accordingly.

Clinical measures and questionnaire assessments at baseline included, resting systolic and diastolic blood pressure calculated as the average of six measurements, including three made supine after 5 minutes

resting; one made standing; and two made sitting, with 5 minutes between measures. Behavioural factors included an inquiry about physical activity, food habits, tobacco chewing, smoking or any other addictions. Study physicians conducted interviews to record history of cardiovascular and metabolic disorders and use of medications for hypertension, heart disease, dyslipidaemias, and other co-morbid conditions. Patients were examined systemically and further they were evaluated with investigations which include CBC, HbA1c, Blood sugar, Liver function tests, lipid profile, Renal function tests, urine for albumin and ECG.

Collection of blood samples and processing

The blood samples of the patients were drawn on arrival (0 hours) and 48 hours from the ante-cubital vein using a 5 ml syringe and immediately mixed in EDTA vacutainers. The samples were tested using the 3-part differentiated automated Haematology analyzer (Sysmex KX-21) and complete blood count analyses of the sample were made including the platelet indices (MPV & PDW). The biochemistry lab samples which includes RFT, LFT, RBS, and lipid profile were taken into the plain vials. HBA1C was collected in EDTA vial and measured by high performance liquid chromatography using Hb Varo machine. Blood glucose was measured with glucose oxidase and peroxidase. Samples from all participants were assayed for total cholesterol measured by end-point enzymatic cholesterol esterase, cholesterol oxidase and peroxidase method, high-density lipoprotein (HDL) measured by end point phosphotungstic acid method, low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL) measured by Fried Wald's formula, and triglycerides using enzymatic lipoprotein lipase, glycerol kinase, glycerol phosphate oxidase and peroxidase endpoint method. All subjects were interviewed and examined as per the prepared proforma, and patients were followed up for the period of 3 months to note any cardio-cerebrovascular events. For comparison samples of 50 diabetics with good glycaemic control were taken as control after matching with sex, age and other co-morbid conditions.

Results

In this study 30 (60%) patients were females, in both study and control group and remaining 20 (40%) were males in both groups Patients included in study group were in the range of 39 to 90 years of age with mean age of 64.4±12.433 years and patients included in the control group were in the range of 39 to 90 year of age with mean age of 63.6±9.901 years which were almost same in both groups.

Table 1: Observations of study group

Parameters		Number of patients	%
Gender	Male	20	40
	Female	30	60
Age (Years)	35-44	02	4
	45-54	07	14
	55-64	12	24
	65-74	15	30
	75-90	14	28
Hypoglycaemia episodes	01	34	68
	02	12	24
	≥3	04	8
HbA1c (%)	≤ 7.5	22	44
	≥7.51	28	56
Serum Creatinine (mg/dl)	≤ 1.4	36	72
	≥ 1.41	14	28
Co-morbidity Factors	NA	06	12
	IHD	17	34
	CVA	01	02
	HTN	14	28
	CKD	14	28
Cardiocerebrovascular Event in Next 3 Months	Present	13	26
	Absent	37	74

In study group there were 34 (68%) patients who had no recurrence of hypoglycaemia whereas 12 (24%) patients had 2 episodes of hypoglycaemia and 04 (08%) patients had ≥3 episodes of hypoglycaemia

during observation time. Among the study group 14 (28%) patients had chronic kidney disease (serum creatinine>1.4) who developed more episodes of hypoglycaemia during observation time.

We also observed that patients on oral hypoglycaemic agents like sulfonylureas group with chronic kidney disease had more episodes of hypoglycaemia during observation period. In study group, 22 (44%) patients had the HbA1c level ≤7.5% and 28 (56%) patients had HbA1c level ≥7.51%. In control group we had taken diabetics with good glycaemic control who had HbA1c level ≤7.5%. We observed that mean HbA1c level of study group was 7.948 ± 1.695 % whereas the mean HbA1c level of control group was 6.841 ± 0.431 %.

In study group, mean of MPV at the time of admission was 10.192±1.265 fl and mean of MPV after 48 hours of admission was 10.332±1.396 which was significantly higher from the control group.We observed that mean of PDW in study group at the time of admission and after 48 hours of admission was 11.396±1.392 fl and 11.516±1.580 fl respectively which was significantly higher from the control group.

Table 2: Distribution of study by variables

Variables	Hypoglycaemic Diabetics (Mean ± SD)	Diabetics with good glycaemic control (Mean ± SD)	p value	Statistically Significant
MPV at admission (fl)	10.192 ±1.265	9.248 ± 0.499	0.0001	Yes
MPV at 48 hours after admission (fl)	10.332 ±1.396	9.320 ±0.516	0.0001	Yes
PDW at admission (fl)	11.396 ±1.393	10.290 ±0.411	0.0001	Yes
PDW at 48 hours after admission (fl)	11.516 ±1.580	10.318 ±0.418	0.0001	Yes

In our study, we observed that both study and control group had certain co-morbid conditions like as ischaemic heart disease, cerebrovascular attack, hypertension and chronic kidney diseases which were 17 (34%), 01(02%), 14 (28%) and 14 (28%) respectively. We observed that mean platelet volume at 48 hours after admission were higher side compared to the mean platelet volume at the time of admission in study group and that were statistically significant (p value - 0.0001). We observed platelet distribution width at 48 hours after admission were higher side compared to the platelet distribution width at the time of admission in study group and that were statistically significant (P value- 0.0001).

Comparison of mean platelet volume (MPV) at the time of admission between both study and control group had shown significant difference. Study group had higher value of MPV ranged from 8.8 to 12.9 fl, whereas control group had MPV ranged from 8.5 to 10.3 fl. Comparison of mean platelet volume (MPV) after 48 hours of admission between both study and control group had shown significant difference. Study group had higher value of MPV ranged from 8.8 to 13.8 fl, whereas control group had MPV ranged from 8.6 to 10.5 fl.

Comparison of platelet distribution width (PDW) at the time of admission between both study and control group had shown significant difference. Study group had higher value of PDW ranged from 9.6 to 15.1fl as compared to control group ranged from 9.7 to 11.3 fl. Comparison of platelet distribution width (PDW) at 48 hours after admission between both study and control group had shown significant difference. Study group had higher value of PDW ranged from 9.5 to 15.2flas compared to control group ranged from 9.5 to 11.7 fl.

We had followed up all the hypoglycaemic and normo-glycaemic diabetics for 3 months and found that 13 (26%) study group patients had developed cardio-cerebrovascular events which includes 03 (06%) cerebrovascular attack, 01 (02%) ACS-UA, 02 (04%) ACS-NSTEMI and 07 (14%) deaths because of cardiovascular events. Whereas 06 (12%) control group had developed cardio-cerebrovascular events which includes 01 (02%) cerebrovascular attack, 01(02%) ACS-UA, 01 (02%) ACS-NSTEMI and 03 (06%) deaths because of cardiovascular events.

In this study we observed that there was significant difference in MPV and PDW in hypoglycaemic and diabetics with good glycaemic control which was statistically significant.

Discussion

Large number of studies till now studied platelet volume indices (MPV & PDW) and platelet count in Ischemic heart disease, ischemic stroke and compared them with healthy control groups. However, there are very few studies like ours regarding effect of hypoglycaemia on platelet indices and clinical outcome.

Alexandra K. Lee, Bethany Warren, Clare J. Lee et al in their study concluded that severe hypoglycaemia was a high-risk state and was followed by a high rate of cardiovascular events and deaths in persons with diabetes in the community. The strong associations of severe hypoglycaemia with coronary heart disease and all-cause mortality persisted after adjustment for a wide range of potential confounders, suggesting that severe hypoglycaemia was a strong risk marker, independent of diabetes severity and standard cardiovascular risk factors.[20] Similarly , in our study we followed up 50 patients for 3 months and found that, 13 patients(26%) had cardio-cerebrovascular events and 7 patients(14%) suffered death.

Study by Shi-Wei Yang, Kyoung-Ha Park and Yu-Jie Zhou et al, demonstrated that Intensive glycaemic control may increase cardiovascular risk and mortality due to hypoglycemia.[21] We found that in our study out of 50 patients, 10 patients (20%) had cardiovascular event, out of which 7 patients (14%) died.

A study by Akash Jain, Sandeep Tak and Manoj Lakhotia et al, demonstrated that severe hypoglycaemia, particularly in type 2 diabetes, was associated with very significant all-cause mortality in short term.[22] We also found that 7 patients (14%) died in 3 months of follow up.

In our study, we observed that study group (hypoglycaemic diabetics) had higher value of platelet indices (MPV & PDW) and 13 (26%) patients developed cardio-cerebrovascular events in next 3 months after having the episode of hypoglycaemia. Whereas, in control group only 06 (12%) patients developed cardio-cerebrovascular events.In study group, out of 13 patients with cardio-cerebrovascular events 03 (06%) had cerebrovascular accident, 01 (02%) had unstable angina, 02 (04%) had NSTEMI and 07 (14%) patients died because of cardiovascular events. In control group, out of 6 patients with cardio-cerebrovascular events 01 (02%) had cerebrovascular accident, 01 (02%) had unstable angina, 01 (02%) had NSTEMI and 03 (06%) patients died because of cardiovascular events.

We also observed that out of 13 patients of study group which had developed cardio-cerebrovascular events, 06 patients had pre-existing ischemic heart disease as the co-morbidity factor. Whereas, out of 06 patients of control group which had developed cardio-cerebrovascular events, 04 patients had pre-existing ischemic heart disease and CVA as the co-morbidity factor. So, we had 07 patients from the study group and 02 patients from the control group which had developed new onset cardio-cerebrovascular events in follow up period of 3 months. We found that there were increased cardio-cerebrovascular events in hypoglycaemic diabetics which was like previous studies.

Cameron et al, Martin et al, Martin et al, Pizzulli et al, MP Ranjith et al, Prem shankerpipliwal et al, G. Ranjani et al, and Vitthal Khode compared MPV between IHD patients and control groups and found that MPV was significantly higher in test groups as compared to control groups.[9-18] A study by Chu H et al, showed that elevated MPV is significantly associated with ACS in patients with acute chest pain and is an early and independent predictor.[23] A review by Chu SG et al, demonstrated that elevated MPV is associated with acute MI, mortality following MI, and restenosis following coronary artery intervention.[24] In a study Gandhi PS et al. 2019, demonstrated that MPV is significantly high in Ischemic heart disease (8.39±1.01 fl) as compared to patients with non-cardiac chest pain.[25] In another study by Manchanda et al, mean of the MPV for the control group was 8.14 ± 0.67fL, for unstable angina it was8.53 ± 0.54fL, 9.67 ± 0.82fL for STEMI & 9.54 ± 0.76fL for NSTEMI.[26] In our study, in study group, mean of MPV at the time of admission was 10.192±1.265 fl and mean of MPV after 48 hours of admission was 10.332±1.396 which was significantly higher from the control group. In the control group, the mean of MPV at the time and after 48 hours of admission was 9.248±0.499fl and 9.320±0.516fl respectively, and these changes were not significant.

A study by Gandhi PS et al, demonstrated that PDW is significantly high in Ischemic heart disease (16.84±1.34fl) as compared to patients with non-cardiac chest pain or healthy subjects (16.22±0.79fl).[25] Similar results were found by Khandekar et al, where 94 patients of ACS were compared to 30 healthy controls.[14] IHD patients had significantly higher PDW (13.19±2.34fl) than healthy controls (10.75±1.42fl).In study by MP Ranjith et al, PDW of 60 patients with ACS was compared with 60 non-cardiac chest pain patients, it was found that PDW in ACS (14.63±0.64fl) was significantly higher than non-cardiac chest pain patients (12.01±0.55fl).[12] In our study, we observed that mean of PDW in study group at the time of admission and after 48 hours of admission was 11.396±1.392fland 11.516±1.580 fl respectively which was significantly higher from the control group. The mean of PDW in control group at the time of admission was 10.290±0.411fl and after 48 hours of admission was 10.318±0.418fl and these changes were not significant.

It is well known that diabetes itself is a risk factor for the occurrence of cardio-cerebrovascular events but in our study, we observed that diabetics experiencing

severe hypoglycaemia have higher value of platelet indices i.e. they have larger platelet volume and are probably more active metabolically. Therefore, larger platelets are more prone to develop cardio-cerebrovascular events in near future as compare to diabetics with good glycaemic control. So, the platelet indices are important, simple, cost-effective and useful in predicting the development of a cardio-cerebrovascular event sometimes in the near future. We suggest use of anti-platelet drugs in patients presenting with severe hypoglycaemia, at least for short to medium term. However, further larger comprehensive studies are required for the confirmation.

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