The Influence of Hyperglycemia at Admission on In-hospital Arrhythmia Patients with Acute Coronary Syndrome

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ABSTRAK

Tujuan: *untuk mengetahui insidens aritmia selama perawatan pada pasien sindrom koroner akut (SKA) dan untuk menilai pengaruh hiperglikemia admisi terhadap kejadian aritmia selama perawatan pasien SKA.* ***Metode:*** *studi kohort retrospektif ini menggunakan rekam medik pasien SKA yang dirawat di intensive coronary care unit (ICCU) RSUPN dr. Cipto Mangunkusumo (RSCM) antara 1 Januari-31 Desember 2014. Hiperglikemia admisi dinyatakan bila kadar gula darah admisi >140 mg/dL. Kejadian aritmia selama perawatan meliputi aritmia atrium, takikardia supraventrikel, blok AV derajat tinggi, dan aritmia ventrikel, yang diobservasi selama 7 hari perawatan.* ***Hasil:*** *Terdapat 232 subjek pada penelitian ini. Prevalensi hiperglikemia admisi sebesar 50,43%. Insidens aritmia selama perawatan adalah 21,55% (IK 95% 16,26-26,84). Analisis bivariat menunjukkan hiperglikemia admisi terkait dengan peningkatan risiko aritmia selama perawatan (RR 1,75; IK 95% 1,04-2,93). Tidak terdapat hubungan antara jenis SKA, diabetes melitus (DM), obesitas, dan hipertensi dengan kejadian aritmia selama perawatan. Analisis multivariat menunjukkan OR hiperglikemia admisi setelah penyesuaian sebesar 2,85 (IK 95% 1,35-6,02), dengan variabel perancu DM.* ***Kesimpulan:*** *insidens aritmia selama perawatan pasien SKA pada penelitian ini adalah 21,55% (IK 95% 16,26-26,84). Hiperglikemia admisi dapat meningkatkan risiko kejadian aritmia selama perawatan pada pasien SKA.*

Kata kunci: *hiperglikemia admisi, kejadian aritmia selama perawatan, sindrom koroner akut.*

ABSTRACT

Aim: *to determine the incidence of in-hospital arrhythmias in patients with acute coronary syndrome (ACS) and to determine the influence of hyperglycemia at admission (HA) on in-hospital arrhythmias complicating ACS.* ***Methods:*** *a retrospective cohort study was conducted using secondary data from medical records of patients with ACS who were admitted to ICCU RSCM, between January 1st-December 31st, 2014. Hyperglycemia at admission was defined when the blood glucose level at admission was >140 mg/dL. The in-hospital arrhythmias encompassed atrial arrhythmia, supraventricular tacchycardia (SVT), high grade AV block (HAVB), and ventricular arrhythmia, during the first seven days of hospitalization.* ***Results:*** *there were 232 subjects in this study. The prevalence of HA was 50.43%. The incidence of in-hospital arrhythmia was 21.55% (95% CI 16.26-26.84). In bivariate analysis, there was significant association between HA and in-hospital arrhythmia (RR 1.75; 95% CI 1.04-2.93). There were no association between type of ACS, diabetes mellitus (DM), obesity, and hypertension, with the in-hospital arrhythmias. In multivariate analysis, the adjusted OR of HA was 2.85 (95% CI 1.35-6.02), and DM was the confounding variable.* ***Conclusion:*** *the incidence of in-hospital arrhythmias in patients with ACS was 21.55% (95% CI 16.26-26.84). Hyperglycemia at admission may increase the risk of in-hospital arrhythmia in patients with ACS.*

Key words: *hyperglycemia at admission; in-hospital arrhythmia; acute coronary syndrome.*

INTRODUCTION

Acute coronary syndrome (ACS) is still a major health problem worldwide.[1] Furthermore, disease- and treatment-related complications affect the outcome. It is urgently needed to determine the early risk identification in reducing the morbidity and mortality.

Arrhythmia is a common complication in patients with ACS. It encompasses atrial arrhythmia, supraventricular tacchycardia (SVT), high grade AV block (HAVB), and ventricular arrhythmia.[2-6] Yet, the incidence of in-hospital arrhythmia in patients with ACS in Indonesia is still unknown. Our preliminary study showed that in-hospital arrhythmia account for the most frequent complication.[7]

Hyperglycemia at admission is commonly found in patients with ACS, regardless the diabetes status. The prevalence of HA ranged from 25-50%. Martalena, et al.[8] revealed that the proportion of hyperglycemia at admission (HA) in patients with ACS at the ICCU RSCM is 43.43%. The underlying mechanisms of HA can be direct due to increasing stress hormone and indirect due to acute or worsening insulin resistance.[9] Hyperglycemia at admission is associated with increased risk of cardiogenic shock,[10] re-infarction,[11] urgent coronary artery bypass graft,[12] and mortality.[13] There have been two studies evaluating the relationship between HA and in-hospital arrhythmias.[5,14] Yet, its causal relationship is unknown.

The ethnics are associated with differences in pattern of coronary heart disease-related risk factors, incidence, and complications.[15] Concerning the magnitude of problems, it urged us to conduct this study in Indonesia's population. Related to glycometabolic response, it was reported that some variables have prognostic values in patients wtih ACS, such as fasting blood glucose,[16] A1c,[17] and mean average blood glucose during hospitalization.[18] We used HA in this study because it is simple, rapid, available in all stages of health care, and routine laboratory examination in patients with ACS.

This study was aimed to determine the incidence of in-hospital arrhythmias in patients with ACS and to determine the influence of HA on in-hospital arrhythmias complicating ACS.

METHODS

The design of our study was retrospective cohort using secondary data from medical records. The subjects were patients with ACS who were admitted to ICCU RSCM, in the period between January 1st - December 31st 2014. The data collection was performed between October and November 2015. The inclusion criteria was patients with ACS. The exclusion criteria were incomplete data, hypoglycemia at admission (<70 mg/dL),[19] arrhythmia at admission, and severe left ventricular dysfunction.

The blood glucose samples were collected within one hour of admission. Blood sugar level was measured using ABX Pentra® machine. Hyperglycemia at admission was defined as blood glucose level at admission >140 mg/dL.[19] In-hospital arrhythmias encompassed atrial arrhythmia, SVT, HAVB, and ventricular arrhythmia in the first seven days of hospitalization through ECG interpretation or events reported in medical record.[20] The confounding variables were type of ACS, obesity, DM, and hypertension.

Data analysis was performed using SPSS version 20. The chi-square test was performed on bivariate analysis. The effect was evaluated and expressed as relative risk (RR). The multivariate analysis was performed using logistic regression test. The effect was evaluated and expressed as adjusted odds ratio (OR).

This study had been approved by the Ethical Committee, Faculty of Medicine, Universitas Indonesia, by the registration number 917/UN2. F1/ETIK/ 2015 on October 19th, 2015.

RESULTS

During the study, there were 332 patients admitted to ICCU RSCM and 284 patients (85.54%) were diagnosed as ACS. As many 52 out of 284 patients were excluded due to two patients with incomplete data, 20 patients with arrhythmia at admission, 29 patients with severe left ventricular dysfunction, and one patient with hypoglycemia at admission.

There were 232 subjects in this study. The prevalence of HA in this study was 50.43%. The incidence of in-hospital arrhythmias was 21.55% (95% CI 16.26-26.84), consisted of atrial

arrhythmia (9.48%), ventricular arrhythmia (7.75%), HAVB (3.45%), and SVT (0.86%) (**Table 1**).

Based on bivariate analysis, there was significant association between HA and in-hospital arrhythmias (RR 1.75; 95% CI 1.04-2.93). There were no relationship between in-hospital arrhythmias and type of ACS (p=0.36), DM (p=0.36), obesity (p=0.73), and hypertension (p=0.54).

Based on multivariate analysis, we found that the adjusted OR for HA was 2.85 (95% CI 1.35-6.02) and DM was the confounding variable associated with the influence of HA on in-hospital arrhythmias (**Table 2**).

Table 1. Baseline characteristics of the subjects (N= 232)

Variables	HA group (n=117)	Non-HA group (n=115)
Sex (male), n (%)	76 (64.96)	77 (66.96)
Age (year), mean (SD)	60.42 (10.48)	60.44 (11.10)
Length of hospitalization (day), mean (SD)	8.07 (3.89)	7.43 (3.40)
Risk factor, n (%)		
- Hypertension	83 (70.94)	71 (61.74)
- Smoking	55 (47.01)	52 (45.22)
- Diabetes Mellitus	70 (59.83)	17 (14.78)
- Dyslipidemia	60 (51.28)	57 (49.56)
- CHD	35 (29.91)	27 (23.48)
- Chronic kidney disease	32 (27.35)	26 (22.61)
- Obesity	47 (40.17)	41 (35.65)
Left ventricular ejection fraction, n (%)		
- Hyperdinamic	11 (9.41)	18 (15.65)
- Normal	65 (55.55)	66 (57.39)
- Mild dysfunction	25 (21.37)	22 (19.13)
- Moderate dysfunction	16 (13.67)	9 (7.83)
Type of ACS, n (%)		
- STEMI	33 (28.20)	25 (21.74)
- NSTEMI	52 (44.44)	33 (28.7)
- UAP	32 (27.35)	57 (49.56)
In-hospital arrhythmias, n (%)	32 (27.35)	18 (15.65)
Type of arrhythmia, n (%)		
- Atrial aritmia	12 (37.50)	10 (55.55)
- SVT	2 (6.25)	0 (0)
- Ventricular arrhythmia	13 (40.62)	5 (27.78)
- HAVB	5 (15.62)	3 (16.67)
Time of the event, n (%)		
- Day 1	16 (13.70)	7 (6.1)
- Day 2	9 (7.70)	5 (4.3)
- Day 3	4 (3.40)	2 (1.7)
- Day 4	2 (1.70)	1 (0.9)
- Day 5	1 (0.90)	0 (0)
- Day 6	0 (0.00)	1 (0.9)
- Day 7	0 (0.00)	2 (1.7)

Table 2. Multivariate analysis of HA, confounding variables, and in-hospital arrhythmias

	P	OR (95% CI)	Δ OR (%)
Crude OR			
HA	0.03	2.03 (1.06-3.87)	-
Adjusted OR			
- Type of ACS	0.04	1.99 (1.04-3.82)	1.67
- DM	0.01	2.86 (1.36-6.02)	43.41
- Hypertension	0.01	2.82 (1.34-5.94)	1.36
- Obesity	0.01	2.85 (1.35-6.02)	1.06

DISCUSSION

Sanjuan, et al.[5] revealed that HA was associated with increased risk of in-hospital ventricular arrhythmia. Koracevic, et al.[14] reported that atrial fibrilllation (AF) was more common in the HA group, compared to non-HA group. Yet, they did not evaluate a casual relationship. This is the first study that evaluates a causal relationship between HA and in-hospital arrhythmias using cohort design. Arrhythmia at admission was excluded.

This study involved 232 subjects. Most of the subjects were male (68.28%), which is consistent with previous studies.[21,22] Mean age of subjects was 60.42 (SD 10.48) years old in HA group and 60.44 (SD 11.10) years old in non-HA group. Some studies reported the same range of mean age of subjects.[21,22] The old age is one of important risk factors in ACS and associated with physiological changes and comorbidities resulted poor prognosis.[23]

We found in this study that the prevalence of HA was 50.43%. Sanjuan, et al.[5] in Spain reported that the proportion of HA was 54.00%, while Ayhan, et al.[24] in Turkey showed that the proportion of HA was 48.3%, and Mansour, et al.[21] revealed that the prevalence of HA in Southern Iraq was 61.70%. These different prevalences reported may be due to the different cut-off value of HA and the sampling method conducted in the studies. Besides, the ethnics seemed to influence the prevalence of HA.

The incidence of in-hospital arrhythmia in this study was 21.55%. Based on the type of arrhythmias, the incidence of atrial arrhythmia was 9.48%, SVT was 9.86%, ventricular arrhythmia was 7.75%, and HAVB was 3.45%. The incidence of atrial arrhythmia in this study differs with Jabre, et al.[25] (6.77%) and Almendro-Delia, et al.[26] (4.00%), due to different duration of observation and sampling method used in the studies. The incidence of SVT in this study differs with Winkler, et al.[27] (13.30%), due to different duration of observation and tools used in identifying the arrhythmias. The incidence of ventricular arrhythmia in this study differs with Hersi, et al.[28] (4.20%) and Sanjuan, et al.[5] (20.00%), due to different exclusion criteria and sampling method used among studies. The incidence of HAVB in this study differs with Singh, et al.[29] (2.90%), due to different exclusion criteria used in the studies.

The Relationship between HA and in-hospital Arrhythmia in Patients with ACS

We found that HA was associated with in-hospital arrhythmias in patients with ACS (RR 1.75; 95% CI 1.04-2.93). It is consistent with the previous studies. Koracevic, et al.[14] reported that AF was more often in HA group significantly, compared to non-HA group (OR 2.07; 95% CI 1.18-3.64). Sanjuan, et al.[5] revealed that HA was associated with ventricular arrhythmia (OR 1.5; 95% CI 1.04-2.30). The underlying mechanisms of this association can be explained in several pathways. First, insulin resistance and acute hyperglycemia increase free fatty acid concentration and affect sympatho-vagal nerve imbalance.[9,30] The lipid accumulation in myocard causes calcium overload, while sympatho-vagal nerve imbalance causes prolonged QT interval. Second, insulin resistance and hyperglycemia inflammation increases in ACS, contributing to both structural and electrical remodeling.[31] Third, hyperglycemia increases free radical production and decreases nitric oxide (NO) production, resulting prolongation of myocardial repolarization, tacchycardia potentiation, decelerated protection from ventricular arrhythmia, and sympathetic modulation of ventricular electrophysiological properties.[30] Fourth, hyperglicemia activates intracrin renin-angiotensin system resulting disturbances in permeability of gap junction, it affects myocardial dysfunction and arrhythmia.[32] Fifth, hyperglycemia increases platelet aggregation causing further processess, including action

potential changes, changes in myocardial contractility, and action potential dispersion.[33]

The Relationship between the Confounding Variables, HA, and the in-hospital Arrhythmia in Patients with ACS

There were some factors considered as confounding variables in this study based on biological mechanisms, which were type of ACS, DM, hypertension, and obesity. Although none of them were statistically significant ($p<0.25$) on bivariate analysis, we proceeded the multivariate analysis based on clinically-importance basis. The multivariate analysis showed that DM is confounding variable in the influence of HA on in-hospital arrhythmia in patients with ACS. It might be due to poor DM status, as shown by Dublin, et al.[34] There are some other mechanisms relating to DM and arrhythmia, including deteriorating inflammation in DM worsens myocardial fibrosis and diastolic dysfunction,[35] DM is related to left atrial dilation and is associated with reentrant electric circuit propagation,[36] and DM is associated with parasympathetic and heterogenous sympathetic denervation.[37]

The Causal Relationship between HA and in-hospital Arrhythmias

We propose a causal relationship between HA and in-hospital arrhythmias. First, we proposed that HA was associated with the in-hospital arrhythmias, because we found that only HA got $p<0.05$ on bivariate analysis. Second, our study result were consistent with previous studies, Sanjuan, et al.[5] and Koracevic, et al.[14] Third, this study specifically defined in-hospital arrhythmias as the outcome, while arrhythmia at admission was excluded. Fourth, this study used cohort design and excluded arrhythmia at admission. We proposed that HA (the cause) preceeded the in-hospital arrhythmias (the event). Fifth, there are some underlying mechanisms revealing biological plaucibility between HA and in-hospital arrhythmias, including increasing FFA concentration and sympatho-vagal nerve imbalance, deteriorating inflammation, increasing free radicals production and decreasing NO production, inducing intracrin renin-angiotensin system, and increasing platelet aggregation.[9,31-34]

Limitation of the Study

This was a retrospective cohort study. It might limit the completeness of supporting data related to risk factors, ECGS, or event reporting.

Despite some limitations, this study may provide good evidence to increase physicians' awareness of HA and higher risk of in-hospital arrhythmias in patients with ACS.

CONCLUSION

The incidence of in-hospital arrhythmias in patients with ACS was 21.55% (95% CI 16.26-26.84). Hyperglycemia at admission may increase the risk of in-hospital arrhythmias.

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