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Abstract

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The effect of glycerin as penetration enhancer in a ketoprofen solid preparation–patch on in vitro penetration study through rat skin

Pratama Ferina Nadya, Umam Choirul, Ameliana Lidya, Nurahmanto Dwi

Category: Medical

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Abstract:

Context: The side effect of Ketoprofen in oral administration is gastrointestinal disorders and kidney failure. The transdermal route can solve this problem, and need penetration enhancer to increase the penetration into the skin. **Aims:** The aims of this study were to determine the effect of glycerin on the penetration of a ketoprofen patch. **Settings and Design:** Four formulas of solid ketoprofen–patch preparation with different amounts of glycerin as a penetration enhancer are tested statistically to observe the

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Effects of soursop leaf extract and physical training on decreasing oxidative stress and pancreatic histopathology in diabetic rat models Retno Yulianti,Citra Ayu Aprilia,Erna Harfiani,Khariri Khairi Pages: 84-95 **DOI:** 10.36295/ASRO.2020.2339 **DOI URL:** http://doi.org/10.36295/ASRO.2020.2339 View Download PDF Download XML	3	12
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Analytical method validation of eperisone hydrochloride in tablet dosage form by tlc–densitometry Vinda Aisya Vira,Nia Kristiningrum, Aisyah Rahmatullah Pages: 105-114 **DOI:** 10.36295/ASRO.2020.23311 **DOI URL:** http://doi.org/10.36295/ASRO.2020.23311 View Download PDF Download XML	1	15

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Elevated blood serum neutrophil collagenase and NADPH oxidase–1 (NOX–1) in acute coronary syndrome

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Abstract
Context: High–level neutrophil activity and oxidative stress were reported in Acute Coronary Syndrome (ACS). **Aims**: This study aimed to analyze serum level neutrophil collagenase (Matrix Metalloproteinase 8, MMP–8) and oxidative enzyme NADPH Oxidase–1 (NOX–1) in ACS. **Settings and Design**: This study an observational cross–sectional study. **Methods and Material**: A total of 84 subjects were studied, consisted of 52 ACS patients (including 21 unstable angina and 15 Non–ST–Segment Elevation Myocardial Infarction [NSTEMI] and 16 ST–Segment Elevation Myocardial Infarction [STEMI]), 16 subjects with stable angina pectoris and 16 healthy control. The level of serum MMP–8 and NOX–1 were analyzed by enzyme–linked immunosorbent assay (Elisa). **Statistical analysis used**: Data were analyzed using Anova and LSD. **Results**: Level serum MMP–8 and NOX–1 were significantly ($p < 0.05$) higher in ACS, the highest level of both markers were found in STEMI patients. Neutrophil leukocytosis was frequently found in STEMI patients as well. **Conclusions**: ACS patients demonstrated sign of inflammation and oxidative stress indicated by elevated serum neutrophil collagenase and NOX–1. These evidences might provide as markers for predicting as well as a guide for preventing and developing therapy for ACS.

Keywords: Angina pectoris, elisa, leukocytosis, matrix metalloproteinase–8 (MMP–8), Segment Elevation Myocardial Infarction (STEMI)

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Introduction

Neutrophil plays an important role in human innate immunity, high neutrophil activities, however, could be detrimental. Normally, neutrophil provides the first line of the body's defense mechanism by phagocytizing, killing, and digesting foreign materials such as bacteria or fungi.[1] This activity, however, could cause neutrophil degranulation and release proteases leading to cause tissue damage.[2]

One of the main important proteases produced by neutrophil is collagenase or Matrix Metalloproteinases (MMPs). Several studies reported increasing level of circulating MMPs in Acute Coronary Syndrome (ACS) patients.[3],[4] MMPs are proteases responsible for the turnover of the intercellular matrix of the tissue structure. MMPs produced as inactive enzymes (pro–MMPs), and its activation can be trigger by oxidative stress.

Considering the contribution of oxidative stress in ACS, therefore it was speculated that increasing level of active MMPs in ACS would be accompanied by increasing level of oxidative enzymes. There was only little study concerned with the role of oxidative enzymes in ACS. One of cell membrane–bound oxidative enzymes, nicotinamide adenine dinucleotide phosphate oxidase 1 (NADPH Oxidase–1 or NOX–1) might increase in ACS. To get a further understanding role of neutrophil and oxidative stress, this study purposed to analyze the serum level of neutrophil collagenase (MMP–8) and (NOX–1) in ACS.

Methods

Materials and research approvals

Elisa kit for human NOX–1 was purchased from Elabscience and MMP–8 from Ray Biotech. The research procedure was approved by the Ethical Committee of Faculty of Medicine University of Jember, Indonesia (Number 1056/H25.1.11/KE/2016). Informed consent was approved by subjects or family of patients. The research design was an observational cross–sectional study.

Subjects

A total of 84 subjects participated in this study were patients from some Hospitals in Jember city, East Java, Indonesia. Subjects consisted of 52 ACS patients (including 21 unstable angina and 15 Non–ST–Segment Elevation Myocardial Infarction [NSTEMI] and 16 ST–Segment Elevation Myocardial Infarction [STEMI]), 16 subjects with stable angina pectoris and 16 healthy control. All of the subjects did not receive antibiotics and anti–inflammatory therapy during the examination.

Serum preparation

From each subject, 10 cc venous peripheral blood was drawn by professional nurse from fossa medianacubiti using veinpuncture. Blood samples were then centrifuged

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for 300 rpm 10 min (1 rpm = 1/60 Hz) for preparing sample serum and then saved in temperature –20 °C until before being analyzed.

Serum level MMP–8 and NOX–1 were analyzed by means of enzyme–linked immunosorbent assay (Elisa), the procedure was done according to the manufacture's instruction. In addition, all of the patients were assessed for complete blood examination, including White Blood Cell (WBC) count, according to the hospital's standard procedure.

Data analysis

Data characteristics of subjects and frequency of leukocytosis were presented descriptively. Anova and LSD were used to analyze the level of MMP–8 and NOX–1.

Result

The characteristic of subjects were presented in Table 1 and Table 1a It was noticed that some data in STEMI patients showed the highest level compared to patients in others group. These parameters were WBC count, % neutrophil, serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT) and Erythrocyte Sedimentation Rate (ESR), while the level of High–Density Lipoprotein (HDL) showed the lowest. ACS was more frequent in males. Hypertension and diabetes mellitus were found in some patients.

Table 1. Characteristic of subjects

No	Characters	Control (N=15)	SAP (N=16)	UAP (N=20)
1	Age	20.93 ± 0.25	64.8 ± 13.53	55.07 ± 7.83
2	Sex (male/Female)	M=4; F=11	M=9; F=7	M=14; F=6
3	Smoker (freq.)	0	6	9
4	Diabetes Mellitus (freq.)	0	4	7
5	Hypertension (freq.)	0	9	9
6	Anti–inflammatory drug	0	0	0
7	Antibiotic drug	0	0	0
8	WBC count	10.03 ± 2.029	9.33 ± 4.2	10.32 ± 3.24
9	% Neutrophil	60.88 ± 7.63	69.98 ± 11.63	64.63 ± 15.06
10	HDL (mg dL^{-1})		57.07 ± 13.87	53.6 ± 14.27
11	LDL (mg dL^{-1})		132.84 ± 29.81	142.4 ± 48.7
12	SGOT (U L^{-1})		52.58 ± 73.62	31.33 ± 15.39
13	SGPT (U L^{-1})		32.58 ± 35.24	32.4 ± 14.1
14	ESR (mm hr^{-1})		13.21 ± 4.61	23.53 ± 18.84

N: Number of subjects; SA: Stable angina pectoris; UAP: Unstable angina pectoris; NSTEMI: Non–ST–segment elevation myocardial infarction; STEMI: ST–segment elevation myocardial infarction.
SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase
HDL: High density lipoprotein; LDL: Low density lipoprotein; ESR: Erythrocyte

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sedimentation rate
WBC: White blood cell; M: Male; F: Female; freq: Frequency

Table 1 a. Characteristic of subjects

No	Characters	NSTEMI (N=15)	STEMI (N=16)
1	Age	64.9 ± 6.4	60.08 ± 10.07
2	Sex (male/Female)	M=11; F=4	M=13; F=3
3	Smoker (freq.)	7	9
4	Diabetes Mellitus (freq.)	6	4
5	Hypertension (freq.)	8	6
6	Anti–inflammatory drug	0	0
7	Antibiotic drug	0	0
8	WBC count	9.89 ± 2.99	14.71 ± 3.25
9	% Neutrophil	69.63 ± 0.08	78.23 ± 14.54
10	HDL (mg dL^{-1})	47.09 ± 9.54	39.03 ± 2.17
11	LDL (mg dL^{-1})	117.81 ± 44.64	127.58 ± 45
12	SGOT (U L^{-1})	66.84 ± 44.1	157.185 ± 193
13	SGPT (U L^{-1})	36.07 ± 21.09	97.31 ± 197
14	ESR (mm hr^{-1})	31.92 ± 10.91	22.88 ± 10.39

N : Number of subjects; SA: Stable angina pectoris; UAP: Unstable angina pectoris; NSTEMI: Non–ST–segment elevation myocardial infarction; STEMI: ST–segment elevation myocardial infarction.
SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase
HDL: High density lipoprotein; LDL: Low density lipoprotein; ESR: Erythrocyte sedimentation rate
WBC: White blood cell; M: Male; F: Female; freq: Frequency

Data concerned with neutrophil showed, besides the highest level of WBC count and neutrophil percentages, the number of patients with leucocytosis was also the highest in STEMI. A total of 86.66 % of STEMI patients demonstrated leukocytosis (Table 2).

Table 2. Frequency of neutrophil leukocytosis in ACS pateints

		Neutrophil leucocytosis	
Groups	**N**	**N**	**%**
Control	16	0	0
Stable angina	16	2	12.50
Unstable angina	21	5	31.25
NSTEMI	15	6	40.00
STEMI	16	13	86.66

N: Number of subject; n: Number of subject with neutrophil leucocytosis
NSTEMI: Non–ST–segment elevation myocardial infarction;
STEMI: ST–segment elevation myocardial infarction

Table 3 presented the serum level of MMP–8 and NOX–1. All of ACS patients expressed significantly higher level ($p < 0.05$) of MMP–8 and NOX–1 compared to

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control (healthy individuals). The highest level was found in STEMI patients, both for MMP–8 and NOX–1.

Table 3. Serum Level of MMP–8 and NOX–1 in ACS Patients

	Serum Level (pg mL^{-1})				
	Control	**Stable angina**	**Unstable angina**	**NSTEMI**	**STEMI**
MMP–8	855.79 ± 1 03.03	1 018.12 ± 182.79[a]	1 120.95 ± 143.43[a]	1 034.54 ± 139.08[a]	1 400.79 ± 145.70[a]
NOX–1	19.10 ± 4.89	21.94 ± 2.88[b]	21.12 ± 2.67 [b]	23.24 ± 4.03 [b]	25.78 ± 4.15 [b]

[a] Significantly different compared to control ($p < 0.05$)

[b] Significantly different compared to control ($p < 0.05$)

Number of Subjects in each group: 15

Discussion

ACS, the leading cause of mortality worldwide [5] is the major clinical manifestations of atherosclerosis. It is including STEMI, NSTEMI, and unstable angina.[6],[7]

Inflammation and oxidative stress are the current acceptable mechanism to explain the pathogenesis of ACS.[6],[8],[9] These mechanisms mainly involve the role of inflammatory cell i.e. neutrophil.[10],[11],[12],[13] Acute neutrophils response against stimulation cause degranulation and release of proteases and other toxic substances that cause tissue damage. In the vulnerable coronary atherosclerotic plaque, neutrophil degranulation leads to the destruction of fibrous cap leading to rupture and subsequently would induce acute luminal thrombosis that can obstruct blood supply into the heart leading to ACS. This study supported the role of neutrophil in ACS. It was indicated by the incidence of neutrophil leukocytosis (86.66 %) in STEMI patients.

In addition to the incidence of neutrophil leukocytosis, ACS patients demonstrated a significant higher ($p < 0.05$) neutrophil collagenase (MMP–8) in this study. Some studies reported the ruptured plaques frequently characterized by highly inflamed, thin and collagen–poor fibrous caps, and contain elevated levels of proteases, including MMPs.[14],[15],[16],[17],[18] The role of MMP–8 in atherosclerotic plaque rupture was highly suspected.[19],[20] Neutrophil collagenase was the member of the MMP family shown to be able to cleave triple–helical collagen fibrils. It is found in specific granules in neutrophils but is also expressed by diverse cell types, including epithelial cells, fibroblasts, macrophages, and endothelial cells. MMPs are a family of Zn^{2+}–dependent endopeptidases. MMPs produced as inactive proenzymes (proMMPs). Its activation can be trigger by other proteolytic enzymes or oxidative stress. In other word, it can be stated that increasing oxidative stress might be followed by increasing activation of MMPs leading to foster tissue destruction.

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A condition of oxidative stress was identified in this study, a significant higher ($p < 0.05$) oxidative enzyme (NOX–1) was shown in ACS patients. The role of oxidative stress as a major contributor to the etiology of ACS have been paid much attention since the last decade. This notion suggested the important role oxidative enzymes such as NADPH oxidases (Noxs) in ACS. Noxs are a class of multicomponent enzymes responsible for the generation of Reactive Oxygen Species (ROS) in inflammatory cells that are interacting with blood vessels.[21] Physiologically Nox–derived ROS contributes to the maintenance of vascular homeostasis. Pathologically, hyperactivity of Nox induces oxidative stress. Nox–derived ROS interact and stimulate other enzymatic sources of oxygen/nitrogen reactive intermediates, and amplify the initial response to insults. In atherosclerosis, Nox–induced lipid peroxidation is highly deleterious and expands the free radical reactions initially produced by activated Nox. Therefore, understanding the molecular mechanisms of Nox regulation, ROS production and its subsequent biological significance, may lead to a focused and effective anti–oxidative stress therapy.[22]

Study Limitation. This was an observational cross–sectional study, the parameters were assessed in one time. The number of subject was limited. Some confounding factors might affect data measurement. A longitudinal study was needed to establish the cause and effect relationship.

Conclusion

ACS patients demonstrated sign of inflammation and oxidative stress indicated by elevated serum MMP–8 and NOX–1. This elevated neutrophil activities might provide as marker for predicting as well as a guide for preventing and developing therapy for ACS.

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