THE EFFECTIVITY OF CAPTOPRIL, LOSARTAN, AND AMLODIPINE ON HYPERTENSION IN RAT MODEL OF GENTAMICIN-INDUCED RENAL FAILURE

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ABSTRACT

Objective: The objective of this study is to compare the effectivity of captopril, losartan, and amlodipine on hypertension in rat model of gentamicin-induced renal failure.

Methods: Adult male Wistar rats weighing 175-225 g are used. The rats were divided into 5 groups: negative control, positive control, captopril 120 mg/kg bw, losartan 20 mg/kg bw, and amlodipine 10 mg/kg bw group. All groups were induced by gentamicin 80 mg/kg bw for 5 days except negative control group. Furthermore, the test preparation was given for 2 weeks.

Results: Serum creatinine was increased in all groups after an induction for 5 days. Renal index control positive, captopril, losartan, and amlodipine groups showed significant differences when compared to the negative control group. Profile of renal histology showed cortical damage to the kidneys. Losartan 20 mg/kg bw group could lower systolic blood pressure when it was compared to the positive control group. Cardiac index losartan group showed significant differences when it was compared to the positive control group. Profile cardiac histology showed the least amount of collagen tissue formation which occurred in the losartan group (4.712%).

Conclusion: The best antihypertensive therapy was demonstrated by losartan 20 mg/kg bw group for hypertension that caused by renal failure compared to positive control group.

Keywords: Amlodipine, Captopril, Gentamicin, Hypertension, Losartan, Renal failure.

INTRODUCTION

One of the difficulties which is encountered of a physician is when it is conducted to the patients who suffer from heart disease and kidney failure simultaneously. Cardiovascular diseases cause of death about 33.3% [1]. The decrease of glomerular filtration rate and proteinuria are the risk factors for the development of cardiovascular disease. Compared to the population, the death is caused by cardiovascular disease on the end stage renal disease (dialysis), 10-30 times higher [2]. In 2006, Smith reported that in 80,098 heart failure patients, 63% worsened the renal function. The level of deterioration of renal function is proportional to the increase in mortality. For every increase of 0.5 mg/dL serum creatinine, there was 15% of increasing in mortality rate [3]. Interaction between organs do not only occur in chronic cases but also in acute renal failure. This reported was by The Cardiovascular Health Study which reported the occurrence of acute renal failure was 3.9% in cardiovascular patients [4].

Based on guideline JNC 7, Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) was a first-line therapy for hypertension with renal failure. Based on the research results in 2011, antihypertensive agents which were used in one of the private hospitals in Indonesia were 32.91% for calcium channel blocker (CCB), 15.82% for ARB, 12.03% for ACEI, and 3.16% for β blockers [5].

MATERIALS AND METHODS

Drugs Used
Gentamicin 40 mg/mL, captopril, losartan, and amlodipine.

Chemical Used
Distilled water, 70% alcohol, hematoxylin-eosin solution, and Masson’s trichrome solution.

Kits Used
Creatinine kit.
Fig. 1: It shows serum creatinine levels before induction (N), after induction (0), on day 7 antihypertensive therapy (7), on day 14 antihypertensive therapy (14); *P<0.05, compared to the negative control using student’s t-test.

The increase of the kidney index indicated kidney damage. The results of kidney index at the end of the test as shown in Figure 2.

Fig. 2: It shows kidney index of animals at the end of the test; *P <0.05, compared to the negative control using student’s t-test.
Fig. 3: It shows profile histological sections of renal cortex at the end of the test with 40x magnification; (a) negative control group, (b) the positive control group after induction; (c) the positive control group at the end of the test; (d) captopril group; (e) losartan group; (f) amlodipine group. An arrow (→) indicates glomerular atrophy.

In this model, the renal failure could lead to the hypertension. The increase in blood pressure that occurred continuously could cause the heart failure. Systolic blood pressure test animals could be seen in Figure 4.

Fig. 4: It shows systolic blood pressure before induction (N), after induction (0), on day 7 antihypertensive therapy (7), on day 14 antihypertensive therapy (14); *P <0.05, compared to the negative control using Student’s t-test; ‘P <0.05, compared to the positive control using Student’s t-test; ‘‘P <0.10, compared to the positive control using student’s t-test.

Fig. 5: It shows cardiac index at the end of the test. *P <0.05, compared to the positive control using Student’s t-test; **P <0.1, compared to the negative control using student’s t-test.
Fig. 6: It shows profile cardiac histology at the end of the test with 100x magnification: (a) negative control group, (b) the positive control group after induction; (c) the positive control group at the end of the test; (d) captopril group; (e) losartan group; (f) amlodipine group. An arrow (→) indicated the collagen network.

Fig. 7: It shows cardiac collagen levels at the end of the test.
DISCUSSION

Based on the results of the study, there was an increase in serum creatinine levels in all induction groups that were positive control, captopril, losartan, and amlodipine group compared to negative control group after 5 days of induction. This suggested that the induction of gentamicin dose of 80 mg/kg bw for 5 days already resulted in renal failure in the animals [6]. The mechanism of intracellular gentamicin nephrotoxicity occurred in the proximal tubule, gentamicin was accumulated in the lysosomes and it formed phospholipidosis lysosomal disorder which was characterized by the activity of phospholipase A1 and sphingomyelinase and intracellular gentamicin nephrotoxicity occurred in the proximal tubules. These meant that the kidney were damaged. Losartan group showed a significant difference (P <0.10). Moreover, losartan to the positive control group using Student’s t-test showed a significant difference (P<0.05).

The continuous high blood pressure could also cause an increase in the synthesis of collagen in the heart. In the heart, collagen had several functions, which were to maintain the thickness and shape of the heart muscle, to protect muscle cells from stretch, and to provide tensile strength to the heart muscle [15].

Extracellular matrix consist of collagen fibrillar lines, the basement membrane, proteoglycans, glycosaminoglycans, and bioactive signaling molecules. Pathway was actively metabolized by collagen and balance between synthesis and degradation. This metabolism occurred during 80-120 days. This cycle was regulated by fibroblasts which were formed from myofibroblasts. Autocrine, paracrine (vasoactive peptides such as angiotensin II and growth factors), and circulatory system-related hormones (aldosterone) were the factors which were responsible to this mechanism. The response of these cells would affect the speed and capacity of the proliferation, migration, and modification synthesizing and producing fibrillar collagen precursors, then the enzyme would change procollagen into collagen to form fibrils and fiber [16].

The analysis of cardiac collagen levels using image analyzer ImageJ software did not show the significant differences between the test groups compared to positive and negative one. Based on these images, it could be seen that the collagen network which was formed in the positive control group and the test group more than the negative control group. This increase occurred because of the increase in blood pressure in the positive control group and the test group. The increased blood pressure could increase the synthesis of collagen in the heart. Hence, the increased collagen synthesis could lead to the accumulation of collagen in the heart so that there was the increase in cardiac collagen.

Synthesis and degradation process of collagen occurred continuously to maintain the balance in the collagen content of the heart. In sum, the presence of elevated levels of collagen was not only caused by an imbalance of the synthesis of collagen which was by fibroblasts and myofibroblasts but also caused by the degradation process by matrix metalloproteinases. In sum, the imbalance could be caused by hemodynamic factors (high blood pressure), nonhemodinamik (hormones), and genetic [17].

In the losartan group, the collagen network formed 4.712% which was less compared to the positive control group and the other test groups. Losartan was angiotensin II receptor antagonist that worked by blocking angiotensin II binding to its receptor. Angiotensin II was a mediator that played a role in the synthesis of collagen tissue. Angiotensin II could induce collagen formation by increasing the production of transforming growth factor-β1 (TGF-β1). Angiotensin II stimulated TGF-β1 gene expression that would induce the formation of collagen type I and type III. Collagen types I and III were common in the heart. When these pathways were inhibited, the formation of collagen tissue would be disrupted [18].

CONCLUSION

Losartan 20 mg/kg bw was the best in lowering systolic blood pressure in renal failure condition compared to positive control group because it had renoprotective effect and might inhibit the formation of collagen network of the heart.
CONFLICT OF INTERESTS
Declared None

REFERENCES