THE EFFECT OF URINARY RETENTION IN THE INCREASED OF PSA EXPRESSION WITHIN PROSTATIC TISSUE

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ABSTRACT

Objective: *To determine whether the increased of PSA expression within prostatic tissue and subsequent systemic blood circulation in acute urinary retention cases of nonmalignant origin were caused by acute inflammation on the prostatic gland. Following this inflammation, PSA will increase, producing by acinar epitelial cells in the gland and continue to capillary vessels before entering the blood circulation.* ***Material & method:*** *Thirty male Rattus Norvegicus were randomly allocated into 3 groups. A control group underwent urethral manipulation, treatment-1 group and -2 group underwent proximal urethral ligation. Prostatectomy was performed after 24 hours in the control and treatment-1 group. Ligation was removed after 24 hours in treatment-2 group, and prostatectomy performed after 4 x 24 hours. Each prostate specimen was examined for PSA expression by immunohistochemistry methods in the prostatic gland. Statistical analysis of study data was analyzed by descriptive statistics and performed ANOVA with level of significance* $\alpha = 0.01$. ***Results:*** *Study results showed an increase PSA expression significantly after urinary retention and returned to normal values four days later after relief of retention.* ***Conclusion:*** *Urinary retention caused acute inflammation on the prostatic gland and increased PSA expression within prostatic tissue. Entry of PSA into stroma and subsequent systemic blood circulation occur through significant increase in PSA production by acinar epithelial cells.*

Key words: *Prostatic tissue, urinary retention, PSA.*

ABSTRAK

Tujuan: *Menentukan apakah peningkatan ekspresi PSA dalam jaringan kelenjar prostat, dan ke sistem sirkulasi darah pada kasus retensio urine akut tidak berbahaya, yang disebabkan oleh inflamasi akut kelenjar prostat. Mengikuti inflamasi ini, PSA akan meningkat, menghasilkan sel epitel byacinar dalam kelenjar dan berlanjut ke pembuluh kapiler sebelum memasuki sirkulasi darah.* ***Bahan & cara:*** *Sebanyak 30 Rattus Norvegicus jantan secara random dibagi menjadi 3 kelompok. Kelompok kontrol menjalani manipulasi uretral, kelompok perlakuan 1 dan 2 menjalani ligasi uretral proksimal. Prostatektomi dilakukan setelah 24 jam pada kelompok kontrol dan kelompok perlakuan 1. Ligasi diambil setelah 24 jam pada kelompok perlakuan 2, dan prostatektomi dilakukan setelah 4 x 24 jam. Setiap spesimen prostat diuji untuk ekspresi PSA menggunakan metode imunohistokimia pada kelenjar prostat. Analisa statistik data penelitian, dianalisa menggunakan statistik deskriptif dan dilakukan ANOVA dengan level signifikan* $\alpha = 0.01$. ***Hasil:*** *Hasil penelitian menunjukkan peningkatan ekspresi PSA secara signifikan setelah retensio urine dan kembali ke nilai normal 4 hari kemudian setelah lepasnya retensi.* ***Simpulan:*** *Retensio urine menyebabkan inflamasi akut pada kelenjar prostat dan meningkatkan ekspresi PSA dalam jaringan prostat. Masuknya PSA kedalam stroma dan lanjutan sistem sirkulasi darah, timbul melalui peningkatan signifikan produksi PSA oleh sel epitel acinar.*

Kata kunci: *Jaringan prostat, retensio urine, PSA.*

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INTRODUCTION

Prostate is a tissue gland which will only be found in men, the place is under the bladder and surrounding urethral prostatic. Recently, there are a lot of acute urinary retention cases which caused by benign prostate enlargement, and followed by the increasing of prostate specific antigen (PSA) serum. To determine the diagnosis of prostate malignant, we performed digital rectal examination, and PSA serum examination. Although there was an increasing on PSA serum, it did not mean that this

increasing was a specific factor to determine the existence of prostate cancer. We have to perform further examination, so that we could determine the existence of prostate malignant, because of the increasing of PSA serum on prostate carcinoma patients, it also found in acute urinary retention and prostatitis.[1] Based on that result, it showed that the increasing of PSA serum has a significant correlation with the incidence of acute urinary retention. At the beginning, PSA was used as indicator to determine the existence of malignant on prostate gland, but in the progress, this examination was not specific for it, because the results of PSA serum examination that exceeding the normal value, also found in BPH and prostatitis patients.[2,3] The mechanism on the increasing of PSA serum was needed for BPH patients with acute urinary retention, so that it could be differed according to PSA serum increasing in prostate carcinoma patients. There were physiologic barrier, to keep the PSA produced by epithelial prostate gland, stay in ductus prostaticus. To reach the PSA systemic sirculation blood in prostate gland, it had to go through prostate gland basalis membrane, prostate gland stroma, and capillary blood vessel basalis membrane around the basal cells and stroma, then it went through systemic blood circulation.[4]

At Soetomo Hospital Surabaya, there were cases of BPH patients with the complication of urinary retention. Urinary retention caused mechanical lesion on prostate gland, then occur the inflammation process.[5,6] The inflammation process would cause the increasing of PSA production by prostate gland acinus epithelial cells.

OBJECTIVE

To analyze the effect of urinary retention on the increasing of PSA expression in prostate tissue.

MATERIAL & METHOD

This was an experimental study using male Rattus Norvegicus which performed proximal urethral total ligation under prostate for 24 hours. This study using post test only control group design.

30 male Rattus Norvegicus were randomly allocated into 3 groups. Group I: Rattus Norvegicus only performed urethral manipulation without ligation. After 24 hours, the prostate tissue was taken to be examined the PSA expression, and it gave the positive reaction on anti-PSA, using immuno-histochemistry method in prostate tissue. Group II: Rattus Norvegicus were performed urethral total ligation using absorbable suture 4.0.

After 24 hours, the urethral ligation was removed, and the prostate gland was taken to examined the PSA expression, and it gave positive reaction on anti-PSA, using immunohistochemistry method in prostate tissue. Group III: Rattus Norvegicus were performed urethral total ligation by using absorbable suture 4.0. After 24 hours, the urethral ligation was removed, then the next 4 x 24 hours, the prostate gland was removed to examined the PSA expression, and it gave the positive reaction on anti-PSA, using immunohistochemistry method in prostate tissue.

To analyze the differences between control group and treatment group were using Anova test with level of significance $\alpha = 0.01$.

RESULTS

From 30 male Rattus Norvegicus during this study, there were none which got sick or dead, so all of them were included in the criteria study. Each of them were performed prostatectomy, control group and treatment group 1 performed 24 hours after manipulation, and treatment group 2 were performed after day-5 (fig. 1).

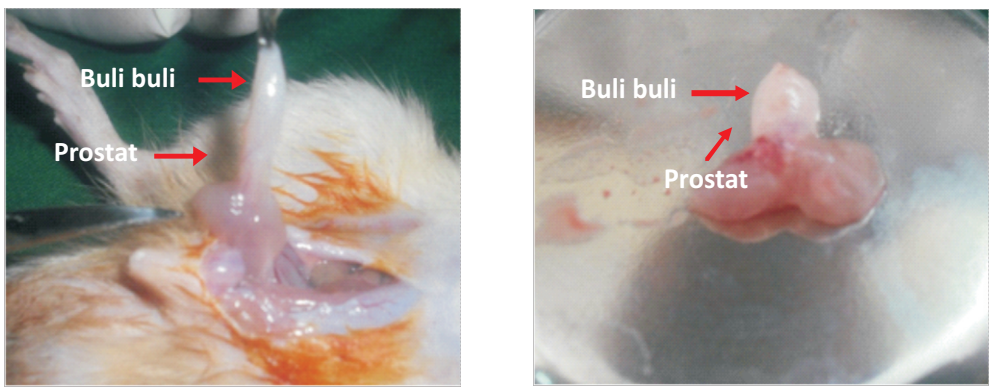

Figure 1. Operation to take prostate specimen (prostatectomy).

Table 1 showed that the white rats weight in all group did not significantly different (homogen) using Anova (p = 0.386), therefore if changes occured in this study, it was because the performed of urethral ligation.

The expression of PSA protein was analyzed based on the existence of brown colour on prostate tissue. The brown colour was as an interpretation of antigen (PSA protein) which binded by its anti-PSA. Antigen-antibody complex would be bound by secunder antibody, labeled biotin, and would be bound by the enzyme, so that the existence of substrate would occuring the brown colour. The examination showed in figure 2 and the calculation was explained in table 5.

Table 2 showed that the higher mean was in treatment group 1, with PSA value 2.92 ± 0.29. The lowest PSA value was in the control group.

The results of data distribution in all group using one-sample Kolmogorov-Smirnov test (table 3). The results showed all of the data distribution was normal ($p > 0.01$), the next test using parametric test.

The difference of mean PSA value was analyzed using one-way ANOVA. Table 4 showed that there were significant difference of mean PSA value ($p < 0.01$) among 3 groups.

Table 1. Homogenity results on white rats weight.

	Group					
	Control		Treatment-1		Treatment-2	
Weight (grams)	214.38	13.212[a]	223.75	20.310 [a]	225.63	22.430 [a]

Note: The same superscript showed not significantly different (p = 0.386).

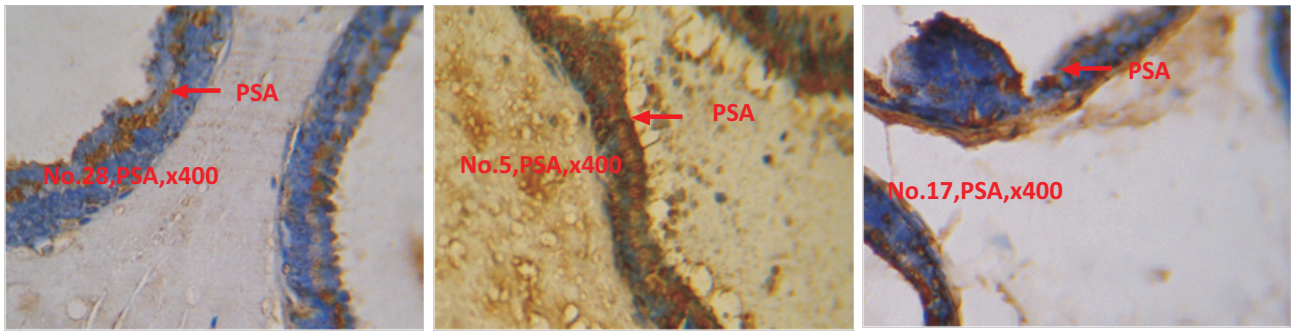

Figure. 2. The immunohistochemistry results on PSA, showed that in treatment group 1 was higher (middle figure) than the other groups.

Table 2. Mean distribution and standard deviation of study data.

	Control		Treatment-1		Treatment-2	
	Mean	SD	Mean	SD	Mean	SD
PSA value	1.67	0.279	2.92	0.290	1.6	0.394

Table 3. The results of PSA value data distribution using One Sample Kolmogorov-Smirnov.

	Control		Treatment-1		Treatment-2	
	Z	p	Z	p	Z	P
PSA value	0.629	0.823	0.557	0.916	0.949	0.329

Table 4. Distribution of One-Way ANOVA result of PSA value.

	Sum of Square	F	P	Description *
PSA value	11.033	52.132	0.0001	S

* S = significant

Table 5. Distribution of double comparation test of mean PSA value expression among 3 groups.

	Control		Treatment-1		Treatment-2	
	Mean Diff	p	Mean Diff	p	Mean Diff	p
Control	-		-1.25	0.0001	0.07	0.881
Treatment-1	-1.25	0.0001	-		1.32	0.0001
Treatment-2	0.07	0.881	1.32	0.0001	-	

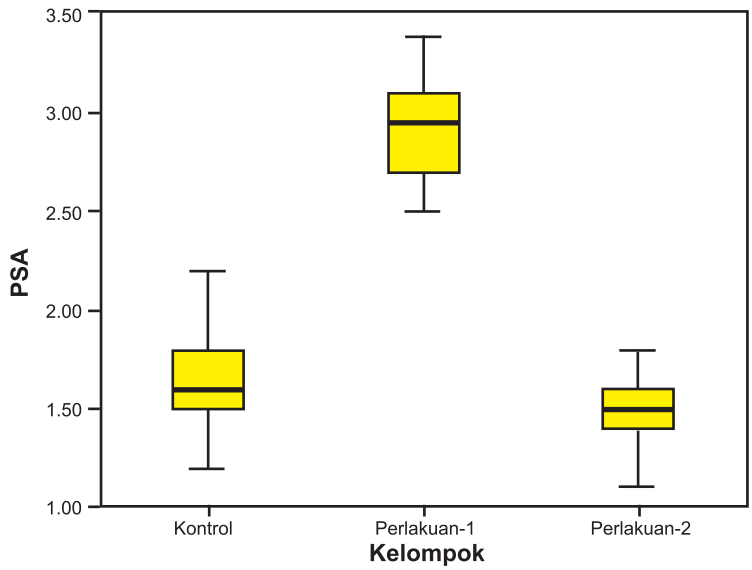

Figure. 3. Histogram of mean PSA expression in prostate tissue, showed the significant increased on treatment group 1 and there were significant decreased in treatment group 2 compared to control group.

To find out the details about the difference of PSA value among 3 groups, it performed double comparation tests using Tukey HSD technique.

Table 5 showed there were significant difference of PSA value between control group and treatment group 1 ($p < 0.01$), but it was not significantly different between control group and treatment group 2 ($p > 0.01$). The results showed that there were significant difference of PSA value between treatment group 1 and treatment group 2 ($p < 0.01$), it also showed on figure 3.

DISCUSSION

Urinary retention is one of mostly occured complication in BPH patients and caused inflammation reaction in prostate tissue. The Urologists often only notice the cause of urinary retention (which is benign prostate hyperplasia) and less notice about the result of it, and the patophysiology of the inflammation reaction. The results of inflammation reaction is the occurring of immunology reaction, nowadays, the urologists are getting interested to analyze it.[6] Although the studies are still on the early stage, it is wellknown that the cause of inflammation reaction is that the prostate gland epithelial cells and stroma cells were giving responds by increasing the production of proinflammation sitokine, such as interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α). The urinary retention also caused the increasing of PSA serum,[7-9] When the PSA increased, it means that the patients were suffering from prostate cancer, because the protein was used as a tumor marker for prostate cancer, so that this incidence would decreasing the sensitifity and specificity of PSA as tumor marker. Until now, there is none who could explain the patophysiology of PSA moving, from inside of prostate gland to the main systemic blood vessel, especially for non-prostate cancer cases, such as the urinary retention cases in this study.

Proinflammation sitokine, such as TNF-α, IL-1β and IL-6, were not expressed in normal organ.

The increasing of production and regulation of sitokine, showed intrinsic responds or innate stress in trauma organ. It was identical with trial animal which performed artificial urinary retention by binding the urethra, so that the trauma or lesion occured in prostate tissue. At the first 1 hour until the next 24 hours, the increasing of sitokine regulation would occur in prostate gland, including the expression of TNF-α, IL-1β and IL-6. Straight stretching in an organ or gland was mechanical lesion, that initiated the increasing of TNF-α and IL-6 production.[5] The increasing of sitokine would be normal if the lesion was not too large. But in this case, the urinary retention with lesion was in all of the prostate tissue, so that the inflammation responds could be excessived. The increasing of sitokine expression caused the increasing of metallo-proteinase matrix enzyme activity in the lesion area, such as MMP-2 and MMP-9.[10]

The increasing of sitokine also could increased fibrosis interstitialis and collagen accumulation in the area outside the lesion. The remodeling process involved synthesis and collagen degradation, as the biggest component of extra-celluler matrix, and the most important thing was, MMP as remodeling mediator. Normally, MMP was in unactive form and it was easy to get activated when the new lesion occured in a few minutes by free radical, sitokine, and in hipoxia tissue condition, and this MMP could be arranged to reach the certain amount by tissue inhibitor of MMP (TIMP). TNF-α and IL-6 could increasing and activating MMP, which at the beginning was responsible for collagen degradation, then the extracellular matrix deposition would occur. In the study of neonates tissue culture on white rats, showed that TNF-α and IL-1β were decreasing the expression of procollagen α1(I), α2(I) and α1(III)mRNA, and increasing MMP-13 (colagenase type I), MMP-2 (gelatinase A), and MMP-9 (gelatinase B), as a result of the urinary retention, the mechanical trauma on prostate gland would occur, then followed with inflammation process, just like that occur in this study. The inflammation process in prostate gland caused the increased of MMP-2 and MMP-9 expressions in prostate gland area, and caused changes on extracellular matrix. After the urinary retention was released, the decreasing of inflammation reaction and the increasing of sitokine would occur, especially the proinflammation, which as an integral component for a respond in tissue trauma, and been proactived in urinary retention cases.[6] The degree of inflammation responds on environment changes was the main factor, that determine the heavy and the light of tissue damage.

The growth and developed tissue, depends on the tissue remodeling and the balance between creating and destructing of extracellular matrix. Extracellular matrix was formed from glycoproteins, collagen, proteoglycans and glycosaminoglycans. The detail structure and the function were different in each of tissue and organs. One of the important extracellular matrix to maintain the tissue formation was basalis membrane. Basalis membrane was extracellular matrix that separating connective tissue with epitel, endotel, muscle fibers and all of the neuron system. The biggest and the main components which forming the basalis membrane was collagen, and the collagen which forming basalis membrane in prostate gland was collagen type IV.

Proteolitic degadration and remodeling extracellular matrix, mostly controlled by super-family from Zn(2+)-dependent extracellular enzymes, which called matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinase (TIMP). MMP was secressed by inflammation cells and stroma cells, as responds of exogen lesion and proinflammation sitokine, such as TNF-α and IL-6. MMP secretion was decreased by some sitokine, such as IFN-γ, IL-4 and IL-10, although the secretion regulation was cells and specific stimulation. MMP was strong influenced by some kind of sitokine and kemokine, which involved in inflammation responds and often had a contrast result at the same time.[11]

Gelatinase A and B were known as kDa and 92 kDa colagenase type IV (MMP-2 and MMP-9), digesting collagen and other extracellular matrix components, including basalis membrane.

Since the first time metalloproteinase matrix was found, as a family proteinase, it became the center of attention for researchers. Matrix metalloproteinase (MMP) was a family of zinc-dependent neutral endopeptidases. Its characteristic was able to perform the degradation of extracellular matrix components, it was also able to perform the degradation in cells membrane and pericellular protein, included cells membrane growth factor precursor, growth factor binding protein, reseptor growth factor receptor, adhesion cells molecule, freezing factors and inhibitor proteinase, also an active form of zymogen.[11-13]

Although at the beginning, only MMP itself involved in the changes and degradation of extra-

cellular matrix, but nowadays the data shows that in doing its function, MMP are working together with sitokine, kemokine, and protein mediator in processing inflammation and immunity.[14] The exact role of MMP in inflammation reaction process and immunity reaction remains unclear, because MMP could increasing and decreasing the inflammation responds.

It is widely known that metalloproteinase is a mediator for trauma incidence, it also has an important function in growing and developing an organ or tissue, it also could remodeling the trauma tissue. The regulation of MMP activity have some phases, transcriptation of gen, activation of proenzyme, and the barrier by non-specific and specific inhibitor enzyme. Tissue inhibitors of metalloproteinase (TIMP) was endogen specific inhibitor of metalloproteinase matrix, that forming inhibitor-enzyme complex.

Nowadays, there are 4 kinds of TIMP, and each of them has a different affinity on specific metalloproteinase. The balance between MMP and TIMP would regulated extracellular matrix remodeling, during the healing process after trauma/lesion incidence. Furthermore, TIMP as a protease inhibitor in its function, also had an important role as signal conductor.

Other study by Baluk P et al, 2004, in white rats which performed micoplasma pulmonis, the inflammation reaction was in the area of breathing and lungs. The result of inflammation reaction was the increased of MMP-2 and MMP-9 expressions.[15] In the other study with immunohistochemistry, showed that MMP-2 was produced endogenly and it came from epithelial cells. The production of MMP-9 was mostly by exogen of infiltration netrofil, but in a small scale, it also found in blood vessel basalis membrane. The majority of blood vessel basalis membrane was also located by collagen type IV. Although the increasing of MMP-2 and MMP-9 expression were high enough, but they could not damage blood vessel basalis membrane or doing the remodeling. It showed that the changes of MMP-2 and MMP-9 expressions in acute inflammation cases, could not damage the extracellular matrix condition or the basalis membrane tissue.

Sitokine, such as tumor necrosis factor-alpha (TNF-α) or interleukin-6 (IL-6) would increased right after tissue trauma (such as ischemia of cardiovascular or brain), and soon it would regulate the process of apoptosis and as an addition initiator in cellular inflammation responds.

In chronic cases, sitokine was as a mediator in repairing and remodeling process, by activating metalloproteinase matrix, collagen forming, to regulate integrin and angiogenesis, it also as a progenitor cells mobilization. The results of proinflammation sitokine effect was useful, such as the healing process and the function of infected organs, but it also could resulted the loss, such as the rupture of basalis membrane gland that got injured, until it did not working like it used to.

The increasing of MMP-2 and MMP-9 in inflammation cases were the results of infection or mechanical lesion, the results were different with the malignant cases (malignant tumor), the gelatinase had an important role in tumor invasion process to the surrounding tissue, until metastase process. Although the tumor invasion and metastase were dynamic, complex and staging process (multi-step), the degradation process in extracellular matrix area as the main support of interstitial matrix and basalis membrane were the main and the first step of the starting of tumor cells invasion to surrounding tissue, and then to further metastase. Basalis membrane, especially extracellular matrix, were mostly consisted of collagen type IV and laminin that useful as a barrier to separate the epithelial cells and stroma tissue (as a support tissue). The basalis membrane components were formed and arranged facing with epithelial cells, and resistance on mostly of interstitial protease. The tumor cells had to go through the basalis membrane barrier a few times to got metastasis process, and the process needed proteolotic enzyme to get through the extracellular matrix components. The straight regulation on MMP activity could prevent the excessive tissue damage. Other study by Ozdemir E et al, 1999, in the role of proteolitic enzyme MMP-2 and -9 in the damage of basalis membrane by performing the degradation of collagen type IV on urothelial tumor, showed that MMP-9 was more dominant in determining the stadium and urothelial tumor gradation compared to MMP-2.[16] The location of MMP-2 and MMP-9 were much more in stroma area than in epithelial tumor cells, especially in surrounding between both tissue. The balance expression between MMP-9 and TIMP-1 in this study were occured in non-damaged basalis membrane. Nowadays, the making of sinthetic inhibitor MMP has been developed, and hopefully, biologically it could be used as therapy to prevent the malignant tumor invasion to surrounding tissue and prevent the metastase. The expression of MMP-9 was very high in other solid tumor cases, such as

glioblastoma and in giant cell tumor at the bones. This study also examined the concentration of MMP-9 and TIMP-1 in urine sampel which showed significant increasing of MMP-9 in invasive tumor cases.

The results of the studies above showed that the roles of MMP-2 and MMP-9 in malignant cases were very dominant in the damaging process or the degradation of basalis membrane, and facilitate the tumor cells to do the invasion to surrounding tissue. There were studies on the importance of MMP role in invasion process and tumor metastase, in vitro and in vivo. In the study on trial animal with prostate cancer, in malignant prostate cells, and in human prostate tissue cells culture, we found the increasing of MMP-2 and MMP-9 concentration, and the reducing of TIMP-1 concentration on epithelial culture media of neoplasia prostate.

A study by Lichtinghagen R et al, 2002, showed that from the examination results of MMP-2, MMP-9 and TIMP-1 expressions, there were the difference between malignant tumor prostate tissue and normal prostate tissue, which had been examined in some aspects.[17] There were different expressions of MMP-2, MMP-9 and TIMP, in mRNA stage and in protein level. There were also differences on mean and rasio of MMP-2 and -9 expressions, on TIMP-1 in malignant tumor prostate tissue compared to the normal one. This study also found that MMP-2 and -9 were supporting and regulating the growth of prostate tumor, by maintained the growth factors in extracellular matrix and also regulated the angiogenesis process in tumor area.

The changes of MMP and TIMP expressions were also found on some malignant incidence in human, such as breast cancer, colon cancer, and lungs malignant. To get the quantitative data, this study using conventional immunohistochemistry technique and densitometry zymografic examination. This study showed that the increasing of MMP-2 and MMP-9 expressions on malignant tumor tissue were higher than non-tumor tissue, so it could supporting the damage of prostate tissue basalis membrane, then the PSA would came out to stroma tissue and then to sistemyc blood circulation. In this study, there were significant increasing of PSA expression on prostate tissue in urinary retention group, but there were no significant damage in basalis membrane, which means that the mechanism of PSA flow-out to stroma tissue, and got to sistemyc blood circulation on prostate gland inflammation cases, caused of urinary retention, as a results of acute prostate inflammation that causing the PSA production by prostate gland asini epithelial significantly increased, so that some part of the PSA went in to the sistemyc blood flew, through the capillary blood vessel in the area surrounding basal cells and prostate tissue stroma. In malignant prostate cases, the developing assumption showed that the PSA flow-out to stroma tissue until systemic circulation, for the results of basalis membrane damage, as the barrier of prostate gland.

The role of MMP-2 and MMP-9 physiologic were to maintain the balance between sintesa and extracellular matrix degradation, during morphogenesis process and embrio differentiation. But in pathologic condition, such as infection process that caused inflammation, and in the process of MMP-2 and MMP-9 malignant production, would significantly increased, but it did not follow with the production of TIMP-1 and TIMP-2, so that the degradation of collagen type IV would occur in basalis membrane.

Prostate gland basalis membrane had some biologic function, as a signal that needed for tissue growth which had been separated, to keep it in a good arrangement. The main component of basalis membrane structure was collagen type IV, which came from mesenkim cells. If there were excessive degradation on collagen type IV, it means there were damage on basalis membrane that caused the damage of epithelial and endothelial cells, so that the materials which produced by epithelial gland would came out to stroma tissue, like that happen to prostate gland with basalis membrane damage, because of prostate cancer growth that caused a lot of PSA flow to stroma tissue, and then went in to the capillary blood vessel.[16,18] But in malignant cases, the PSA flew-out from prostate gland to capillary blood vessel because of urinary retention, it did not go through the damage of the basalis membrane gland, like that happen in prostate malignant cases.

Prostate specific antigen (PSA) had been widely known as a serum marker in prostate cancer, but it had low specificity because on benign or inflammation prostate, showed the increasing of PSA serum.[19] The increasing of PSA expression in prostate tissue until systemic circulation on prostate cancer, was suspected because of the damage of basalis membrane gland,[18] But there was no study showed what causes the increasing of PSA flow-out from the inside of prostate gland to stroma tissue until systemic circulation in benign prostate with

inflammation. The exact mechanism of the PSA expression were increase in stroma tissue, to systemic circulation in acute urinary retention cases, had not been known yet, some study said that it was because of the infark in prostate gland, but it did not been proved yet.[9] Based on that study, there were the increasing of mean PSA serum value, twice higher than PSA serum value one week after the urinary retention was released. A study by Semjonow et al, 1996, the result of PSA serum examination was decreased 50% after the urinary retention was released in 24-48 hours later.[20] This study result showed the significant increasing of PSA expression because of urinary retention. Then the PSA examination in prostate tissue was performed 4 days after the urinary retention was released, and it showed the significant decreasing of PSA, which means that PSA value was the same as before the urinary retention occur (tabel 5). It showed that the half time of PSA was 2x24 hours, like the previous study. [9,20]

In benign prostate the percentage of free PSA expression was higher than prostate carcinoma, and the half time of free PSA was only about 2-3 hours, so it was understandable that the decreasing of PSA expression on benign prostate with urinary retention was faster, after the retention was released.[9]

CONCLUSION

This study proved that urinary retention resulted the incidence of inflammation reaction (inflammation responds). It showed that the inflammation reaction resulted PSA production by the significant increasing of prostate gland asini epithelial cells, and the normal PSA value 4 days after the urinary retention was released, so it can be concluded that the PSA flow-out from inside of the prostate gland to stroma area until systemic circulation, it was because of the urinary retention did not go through the damage of prostate gland membrane basal, but the production of PSA by prostate gland asini epithelial cells which significantly increased.

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