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### Utilization of furosemide to increase urine production as a negative contrast media in CT urography

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#### ABSTRACT

Non-contrast CT scan is a mainstay in diagnosing urolithiasis and obstruction of the urinary tract. In diagnosing urolithiasis, non-contrast CT scan needs tracking images to distinguish urolithiasis from appendicolith, phlebolith, or calcification in the iliac artery. The making process of tracking is difficult due to the small size of the ureter and isodense with the intestine and psoas muscle. CT urography is generally carried out with iodine contrast media, but in patients with contraindications to iodine, trypanophobia and lack of funds, CT urography fails. The author intended to do a study using urine as a negative contrast medium, a substitute for iodine contrast media. This study aims to identify differences in the degree of distention and density of the urinary tract between pre-diuretic and post-diuretic using 40 mg of furosemide tablet as a diuretic agent.

This study type was pre-experiment with one group pretest-posttest design. Measurement of distention and the degree of density was performed on coronal image tracking of urinary tract CT urography pre and post diuretic by using Measured Distance software to determine the degree of distention and Region of Interest software to determine the density of the urinary tract. Data analysis used paired t test with a 95% significance level.

The results showed that there were significant differences in the degree of distention and density of the urinary tract between pre-diuretic and post-diuretic with the p values of the degree of distention of right renal pelvis of 0.001, right ureter of <0.001, left renal pelvis of 0.002, left ureter of 0.001, and the p values of the density of right renal pelvis of <0.001, right ureter of 0.003, left renal pelvis of 0.001, left ureter of <0.001.

Administration of 40 mg of furosemide tablets to CT urography patients could increase the degree of distention and reduce the density of the urinary tract.

**Keywords:** Furosemide, Urine, Degree of distension, Density.

#### INTRODUCTION

Over the past few decades, Intravenous Urography (IVU) has become a mainstay in diagnosing urolithiasis and obstruction of the urinary tract. Along with the development of

imaging modalities, most of these IVU examinations were replaced by non-contrast CT Scan examination. [1] In diagnosing urolithiasis in non-contrast CT scan it is necessary to make coronal tracking images using the Curved Planar

Reformation (CPR) software to distinguish urolithiasis from appendicolith, phlebolith, or calcification in the iliac artery.

Based on the observation conducted by the author at the Radiology Installation at Salatiga Regional General Hospital, tracking on abdominal non-contrast CT scan was difficult to perform and sometimes could not be done due to the small size of the ureter and isodense with the intestine and psoas muscle.

The European Society of Urogenital Radiology (ESUR) defines CT urography as a diagnostic examination to show kidney, ureter, and urinary bladder using CT scan with thin pieces and intravenous injection of contrast media in the excretion phase. [2] CT urographic examination results with iodine positive contrast media can assess renal, ureteric, and vesic urinary function as well as evaluate hydronephrosis, hydroureter, urolithiasis, nephrolithiasis, hematuria, and detect stones or tumors in the urinary tract.[3]

CT urography using iodine contrast media has contraindications, among others, for patients with kidney failure, patients who experience severe reactions to previous examinations and patients who are pregnant. [4] Non ionic iodine contrast media used on CT urography is much more expensive than ionic iodine contrast media. [5]

Urine is a residual fluid excreted by the kidneys which is then released from the body through the process of urinalization. The composition of urine consists of 96% of water and 4% of solid objects in the form of urea 2% and other metabolic products 2%. [6] The amount of urine production is around 900-1500 mL/24 hours or 37.5-62.5 mL/hour. [7]

Administration of diuretic furosemide drugs could increase urine production to 1542 mL/h in peak reactions. [8] The effect of giving furosemide could increase urine production to reach 24.67 to 41.12 times of urine production under normal conditions. [7, 8]

Based on the observation conducted by the author in Salatiga Regional General Hospital, there were CT urographic patients who had contraindication to iodine contrast media and patients who had trypanophobia, which caused CT urography with iodine contrast media failed. The cost of CT urography examination with iodine positive contrast media was also relatively expensive.

From those problems, a CT urography examination will be carried out by utilizing urine excreted by the kidneys as a negative contrast medium because 96% urine composition is water, and 40 mg of oral furosemide tablet was used as the diuretic agent. This examination was carried out with two time scannings, namely pre-diuretic as pre-contrast and post-diuretic as excretion phase (post contrast) with an expectation that there would be a difference in the degree of distension and density of the urinary tract before and after administration of 40 mg of oral furosemide tablet.

The difference in the degree of distension and density of the urinary tract before and after administration of oral furosemide was due to an increase in urine volume that filled the lumen of the urinary tract because of the diuresis effect of furosemide. The increase in the volume of urine that passed through the urinary tract was characterized by an increase in the degree of distension and a decrease in the density of the urinary tract. The difference in the degree of distension and density of the urinary tract could be use to assess the anatomy of the urinary tract. Furthermore, it can also be used to assess the function of the urinary tract in passing urine from the kidneys to urinary bladder, as well as to diagnose hydroureter.

Oral furosemide was chosen as a diuretic agent because oral furosemide is known to be effective, rapidly cause diuresis effect, and it is cheap. The cheap price of oral furosemide makes the cost of CT urography examination more affordable. The use of oral furosemide which does not require medical treatment such as injection allows CT urography to be performed in patients with trypanophobia. CT urography examination with administration of oral furosemide can also be carried out in patients with renal failure and have allergy to iodine contrast media.

This study aims to prove that administration of oral furosemide could increase the degree of distension and could reduce the density of the urinary tract during CT urography examination.

## **MATERIALS AND METHODS**

This study was a pre-experiment study with one group pretest-posttest design. This study aims to determine the differences in the degree of distension and density of the urinary tract before

intervention (pre-test) and after intervention (post-test) among the study samples.

The study was conducted by giving two interventions to patients with CT urography, namely pre-diuretic scanning and post-diuretic scanning. Pre diuretic scanning was scanning without furosemide and post-diuretic scanning was scanning by administering 40 mg of furosemide tablet orally one hour before post diuretic scanning. Administration of 40 mg of tablet furosemide orally to CT urography patients was intended to increase urine production as a negative contrast medium, because it can increase the degree of distension and decrease the density of the urinary tract.

After pre and post diuretic scannings were completed, then post processing was done by making coronal tracking images using CPR software from the kidneys, renal pelvis, ureters, to urinary bladder. The CT urography coronal tracking results of pre and post diuretic produced were validated by the radiologist first, then the radiographers measured the diameter of the renal pelvis and ureter with Measured Distance software to determine the degree of distension and measured the density level in the form of CT Number on the renal pelvis and ureter by using ROI software to determine the density.

Measurement of the degree of distension and density of urinary tract coronal image tracking of pre and post diuretic was done by 3 radiographers who had the competence and authority to conduct CT urography, namely radiographers with a minimum of 5 years of service and had credential certificates to conduct plain CT urography.

The independent variable in this study was furosemide, the dependent variable was urine, and the confounding variables were ADH hormone, insulin hormone, nerve, age, diuretic substance, environmental temperature, psychological condition, amount of water drunk, life style and

activity. Measurement of dependent variable of urine was conducted by measuring the degree of distension and density of the renal pelvis and ureter.

The samples in this study were CT urographic patients who met the inclusion criteria, namely plain CT urography patients with clinical urinary tract obstruction aged 30-60 years, and were not included in the exclusion criteria, namely pregnant women, patients with kidney failure and diabetes mellitus, patients who consumed drinks containing diuretic substances, and patients with contraindications to furosemide. The number of samples was 16 patients, selected by consecutive sampling, non probability.

Instruments used in this study included CT Scan of Hitachi Type Eclos 8 which was equipped with Curved Planar Reformation (CPR) software, Measured Distance software, and Region of Interest (ROI) Settings software, and AC. Materials used here were questionnaire to control the confounding variables, informed consent form, 1 L packaged drinking water, and 40 mg of oral furosemide.

Data analysis was performed using paired statistical test with the consideration that the data were 1 ratio data and were normally distributed. If the data distribution was not normal, data analysis was performed using Wilcoxon test with a 95% confidence level.

## RESULTS AND DISCUSSION

The samples of plain CT urography patients in this study amounted to 16 people with 12 male patients and 4 female patients, patients with the age range of 30-40 years were 5 people, 41-50 were 6 people, and 51-60 were 5 people. To make the age factor did not affect urine production, this study only included patients aged 30-60 years.

**Table 1. Results of degree of distension measurement**

Anatomical part	Degree of distension	
	Pre-diuretic	Post-diuretic
1 Right renal pelvis	8,51 ± 6,06	13,81 ± 6,17
2 Right ureter	2,66 ± 1,65	4,85 ± 2,05
3 Left renal pelvis	13,16 ± 11,02	18,32 ± 12,28
4 Left ureter	4,04 ± 2,42	5,42 ± 2,10

The results of the degree of distension measurement with two interventions of pre-diuretic and post-diuretic scanning showed that the mean value of post-diuretic distension in the CT urography coronal tracking images in the renal pelvis and ureter was higher than the pre-diuretic degree of distension.

The results of the degree of distension measurement showed a fairly high standard deviation value. This high standard deviation was due to the lack of clinical control of hydronephrosis/hydroureter patients based on grade and the location of the abnormalities in the right or left renal pelvis and ureter. Measurement of the degree of distension was performed on the right

and left urinary tracts both with hydronephrosis/hydroureter and normal, whereas CT urography patients with clinical hydronephrosis/hydroureter usually had it on one side only and with various grades.

Patients with hydronephrosis or hydroureter without furosemide showed wider diameter of the renal pelvis and ureter compared to the normal size because they contained more urine due to obstruction. The width of the diameter of the renal pelvis and ureter also depended on the grade of hydronephrosis/hydroureter. The varied results of the clinical measurement of urinary tract samples caused the high standard deviation.



Figure 1. Pre-diuretic distension measurement of the right urinary tract



Figure 2. Post-diuretic degree of distension measurement of the right urinary tract.

Table 2. Difference test results of pre-diuretic and post-diuretic degree of distension measurement

Independent Variable	Dependent Variable	P value
	Degree of distension	
Administration of 40 mg diuretic of oral furosemide	1 Right renal pelvis	0,001
	2 Left renal pelvis	0,002
	3 Right Ureter	< 0,001
	4 Left Ureter	0,001

It can be seen in the table above that the p value of the degree of distension variable in the right renal pelvis was 0.001, the left renal pelvis was 0.002, the right ureter was <0.001, and the left ureter was 0.001. Thus, the conclusion was that there was a significant difference in the degree of distension of the right renal pelvis, the left renal pelvis, the right ureter and the left ureter in CT urography coronal tracking images between pre-diuretic scanning and post-diuretic scanning interventions.

The difference in the degree of urinary tract distension between pre-diuretic and post-diuretic interventions was due to the effect of providing 40 mg of oral furosemide to patients performed 1 hour before post-diuretic scanning. Administration of 40 mg of oral furosemide tablets to patients 1 hour before CT urography post-diuretic scanning will affect the increase in urine volume produced by the kidneys. Furosemide works on the Henle kidney by inhibiting sodium and chloride reabsorption into

the circulation and removing it from the body through increased urine production.[9]

Administration of furosemide can increase urine production to 1542 mL/h in its peak reaction, which is 1 hour after oral administration, while urine production in human is normally 37.5-62.5 mL/hour. [7,8] There is an increase in urine production which reaches 24.67 to 41.12 times which causes the renal pelvis and ureters to be distended/increased in diameter due to a dramatic increase in urine volume in the renal pelvic cavity and ureter.

Nolte-Ernsting CC et al (2001) stated that administration of furosemide could improve opacification to be more complete of 30/32 (94%) in the ureter and 32/32 (100%) in pelvicaliceal system due to the dilution of iodine contrast media by urine. [10] McTavish JD et al (2002) and Nolte-Ernsting CC et al (2001) did not use degree of distension parameter in their study, but they used the opacification parameter of renal collecting system and ureter as criteria to evaluate. [10,11]

**Table 3. Results of density measurement**

Anatomical part	Density	
	Pre diuretic	Post diuretic
1 Right renal pelvis	15,67 ± 7,86	-3,56 ± 7,04
2 Right ureter	10,75 ± 12,47	-5,03 ± 8,35
3 Left renal pelvis	13,82 ± 9,57	0,08 ± 7,01
4 Left ureter	14,61 ± 7,75	0,76 ± 7,18

The results of density measurement on CT urography coronal tracking images with two interventions namely pre-diuretic and post-diuretic scanning showed that the mean of post-diuretic density of CT urography coronal tracking image on the renal pelvis and ureter was lower than pre-diuretic density.

The results of density measurement showed that the standard deviation value was quite high. This high standard deviation was due to the lack of clinical control of hydronephrosis/hydroureter patients based on grade and the location of the abnormalities in the right or left renal pelvis and ureter. Density measurement in this study was

carried out on the right and left urinary tract both with hydronephrosis/hydroureter and normal, whereas CT urography patients with clinical hydronephrosis and hydroureter usually had it only on one side only.

Patients with hydronephrosis and hydroureter without furosemide had more urine in the form of water in the renal pelvis and ureter, which was lower in density than the lumen of the renal pelvis and ureter which is muscle, compared to the normal renal pelvis and ureter. The standard deviation became high due to these varying clinical measurement results of urinary tract samples.



Figure 3. Pre-diuretic density measurement of the right urinary tract.

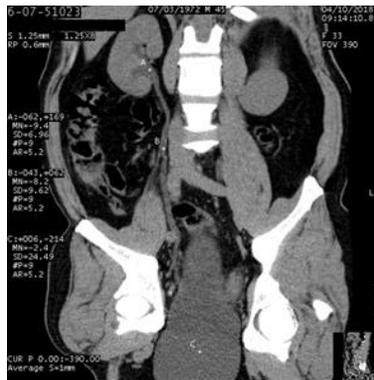


Figure 4. Post-diuretic density measurement of the right urinary tract

Table 4. Difference test results of pre diuretic and post diuretic density degrees measurement

Independent Variable	Dependent Variable	P value
	Density	
Administration of 40 mg diureticof oral furosemide	1 Right renal pelvis	< 0,001
	2 Left renal pelvis	0,001
	3 Right Ureter	0,003
	4 Left Ureter	< 0,001

It can be seen in the table above that the p value of the density variable of the right renal pelvis was <0.001, the left renal pelvis was 0.001, the right ureter is 0.003, and the left ureter was <0.001, so the conclusion was that there was a significant difference in the density of the right renal pelvis, the left renal pelvis, the right ureter and the left ureter in CT urography coronal tracking images between pre-diuretic scanning and post-diuretic scanning interventions.

The difference in the density of the urinary tract between pre-diuretic and post-diuretic interventions was due to the drastic increase in urine volume due to the effect of providing 40 mg of oral furosemide which resulted in the distended urinary tract lumen because it contained more urine than usual. This

resulted in a decreased density in the central area of the renal pelvis and ureter because urine contains 96% of water with a lower density of 0.993681 gr/cm<sup>3</sup> compared to density of renal pelvis lumen and ureter that are muscles of 1.000000 gr/cm<sup>3</sup>. [12-15]

This decreased density simultaneously also decreased the linear attenuation coefficient of the central area of renal pelvis and ureter in the form of a decrease in the CT Number value in CT urography coronal tracking images. The CT Number value of a tissue is directly proportional to the density and linear attenuation coefficient ( $\mu$ ) of the tissue. [16,17] Urine in the form of water has a CT Number of 0 HU and a linear attenuation coefficient of 0.206 cm<sup>-1</sup>, while the lumen of the

renal pelvis in the form of muscle has a CT number of 50 HU and a linear attenuation coefficient of  $0.237 \text{ cm}^{-1}$ . [12-15]

Previous studies conducted by Nolte-Ernsting CC et al., 2001; Paz RCM et al., 2010; Van Der Molen AJ et al., 2008 showed that intravenous injection of a low-dose diuretic drug (10 mg furosemide) which could increase urine production, before injecting contrast media, would cause a decrease in density and a more homogeneous collecting system opacification compared to saline administration because there was dilution of iodine contrast media by urine. [2,10,11,18]

In previous studies conducted by Nolte-Ernsting CC et al., 2001; Paz RCM et al., 2010; and Van Der Molen AJ et al., 2008, the use of furosemide which could increase urine production was used to dilute iodine contrast media on CT urography with positive contrast media to obtain a more complete, homogeneous collecting system opacification, and can minimize beam hardening artifact on intrarenal collecting system. [2,10,18] In this study, the author utilized the increase in urine production as a negative contrast medium because it contains 96% of water with a lower density ( $0.993681 \text{ gr/cm}^3$ ) compared to the lumen of the renal pelvis and ureter in the form of muscle/soft tissue ( $1.000000 \text{ gr/cm}^3$ ).

In previous studies conducted by Nolte-Ernsting CC et al., 2001; McTavish JD et al., 2002; Paz RCM et al., 2010; and Van Der Molen AJ et al., 2008, the administration of furosemide was carried out intravenously. [2,10,11,18] In this study, the author used oral furosemide tablet because oral furosemide is known to be effective, rapidly cause diuresis effect, and it is cheap. The cheap price of oral furosemide makes the cost of CT urography examination more affordable. The use of oral furosemide which does not require medical treatment such as injection allows CT urography to be performed in patients with trypanophobia. CT urography examination with administration of oral furosemide can also be carried out in patients with renal failure and have allergy to iodine contrast media.

Administration of diuretic in the form of 40 mg of furosemide tablet orally to CT urography patients can provide benefits as well as contraindications, especially for patients with precoma condition due to liver cirrhosis and kidney failure with anuria. Administration of furosemide

also has a risk to cause hypokalemia and hyponatremia, worsen diabetes mellitus and gout, liver failure, enlarged prostate, and porphyria. [19]

Furosemide is safe to use on CT urography since there have been no reports of adverse reactions associated with furosemide administration during nuclear medicine or MRI, but with the many contraindications and risks of giving furosemide, it is necessary to look for natural diuretics that are less contraindication and risks. [20] Drinks that contain diuretic substances such as tea or coffee can inhibit the reabsorption of  $\text{Na}^+$  ions which cause the ADH hormone to decrease so that water reabsorption is inhibited and urine volume increases. [21]

The peak diuretic reaction occurred between 30 to 90 minutes after administration of the oral furosemide tablet, and the reaction would disappear within 4 hours. [19] In this study, administration of 40 mg of furosemide tablet orally to CT urography patients was performed 1 hour before post-diuretic scanning. With this long time peak reaction period of furosemide, which was 30 to 90 minutes, it is necessary to find the actual peak reaction time of furosemide so that the degree of distention and density of the urinary tract can be more optimal.

This study was a pre-experiment study because the samples were not randomly selected and confounding variables could not be controlled by the author, so that it still allowed the existence of external variables that affected the dependent variable.

In this study, the author intended to know the effect of providing 40 mg of tablet furosemide orally to CT urography patients to increase urine production, as measured by the parameters of the degree of distention and density of the urinary tract. The increase in urine production was influenced by the administration of furosemide and was also influenced by confounding variables namely ADH hormone, insulin hormone, nerve, age, diuretic substances, environmental temperature, psychological condition, amount of water drunk, life style and activity, so that the confounding variables must be controlled in such a way that it would not affect the dependent variable of urine production.

Because of the limitations of time and resources, the author was unable to control the confounding variables, namely ADH, nerve, and psychological conditions of the patients, so that

these variables were allowed to influence the increase in urine production.

## CONCLUSIONS AND RECOMMENDATIONS

Based on the results of study that has been conducted it can be concluded that the administration of diuretics in the form of 40 mg of oral furosemide tablet for the CT urography patients could increase the degree of distention and reduce the density of the urinary tract.

To make it easier for radiographers to track CT urography and help diagnose hydronephrosis while assessing the function of the urinary tract in passing urine from the kidney to the vesic urinaria during plain CT urography examination, pre and post diuretic scanning with oral furosemide as a diuretic agent is recommended.

To improve the precision and accuracy of the study results and obtain optimal degree of distention and density regarding the use of

furosemide on CT urography, similar studies can be conducted with a greater diuretic substances variation and time variation, and a tighter clinical control of patients.

The future similar studies can be conducted by using natural non-chemical diuretics such as coffee or tea, so there are fewer contraindications and side effects than the use of furosemide.

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