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Research Article

Dutasteride and Lycopene Combination for Bleeding Control in Post Transurethral Resection of Prostate Evaluated by VEGF Expression and Hemoglobin Level

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ABSTRACT

Background and Objective: Bleeding is a complication that can happen during transurethral resection of the prostate (TURP) or post surgery. Dutasteride and lycopene can reduce the rate of bleeding complication in benign prostate hyperplasia (BPH). The study aims to analyze the effect of combination of dutasteride and lycopene in decreasing the amount of bleeding in BPH patients underwent TURP.

Materials and Methods: The study is an experimental double blind randomized control trial post test only. It was performed by comparing changes in angiogenesis with VEGF expression and hemoglobin levels as the parameters. The study divided the sample into 2 groups of BPH patients underwent TURP; the first group was given Dutasteride 0.5 mg once daily combined with lycopene 30 mg once daily 30 days prior to surgery and the second group was given Dutasteride 0.5 mg only. **Results:** Combination of dutasteride and lycopene was not significant in reducing VEGF expressions, as evidenced by the results of statistical tests with Independent t-test in 2 groups which obtained $p = 0.43$. Mean data of hemoglobin level in each group showed significant result with $p = 0.00$. **Conclusion:** Combination of Dutasteride and lycopene 30 days prior to TURP surgery is not significant compared to Dutasteride alone in decreasing VEGF expression, but there was a significant result in Hemoglobin level comparison between pre and post operative.

Key words: Dutasteride, lycopene, benign prostate hyperplasia, transurethral resection, hemoglobin, vascular endothelial growth factor

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Benign prostate hyperplasia (BPH) is frequently found in elderly men. Clinical symptoms that appear can interfere with the patient's daily activities. Along with the increase of human life expectancy, the elderly human population will also increase. This leads to the incidence of BPH associated with lower urinary tract symptoms (LUTS) and urinary retention which also will experience an increase from 5 million sufferers to 9 million sufferers by 2025. The cause of BPH is not yet known clearly, but until now it was caused by a decrease in hormone levels in men due to the aging process, especially testosterone. The testosterone hormone in the prostate gland will be converted to dihydrotestosterone (DHT). The DHT then will chronically stimulate the prostate gland making the prostate gland enlarged¹.

Operative and medical therapies have been carried out in patients with BPH. The frequently performed operative therapy is transurethral resection of the prostate (TURP). TURP is one of the standard operations to relieve symptoms of LUTS and urinary retention in patients with BPH. Complication that often occurs during TURP and post-surgery is bleeding which will lead to the increase in morbidity and mortality rates. Some studies have reported that the number of blood needs during TURP surgery varies between 1-10%². The amount of bleeding occurred during surgery depends on prostate volume, duration of action, operator skills and the presence of comorbid factors such as diabetes mellitus, hypertension etc³.

Various studies have been developed to investigate angiogenesis (anti angiogenic) inhibiting factors, one of which is therapy with a 5 α reductase inhibitor that impedes the conversion of testosterone to dihydrotestosterone (DHT) needed for enlargement of the prostate gland^{4,5}. The 5 α reductase inhibitor drug can reduce the expression of vascular endothelial growth factor (VEGF) in the subepithelial tissue of the prostate and prevent spontaneous bleeding in BPH^{6,7}. Research carried out on the prostate had an effect on dutasteride to reduce the rate of bleeding complications in BPH with the mechanism of reducing the prostate gland and increasing the stability of blood vessel walls, compared to only decreasing vascularity⁸. Study in 2004 found that administration of finasteride before TURP will decrease hemoglobin more minimally and patients do not require transfusion compared to the control group (without finasteride)⁹. Some mechanisms of 5 α reductase inhibitors are such as reducing androgen dependent angiogenic growth factors like VEGF, reducing sub urothelial microvessel density and decreasing blood vessel flow causing the prostate gland to shrink, and inducing apoptosis⁴.

Lycopene is one of the other therapies to suppress angiogenesis. Lycopene has a red pigment carotenoid found in tomatoes and other red fruits¹⁰. Lycopene is a potential compound for anticancer and contains antioxidant activity two times stronger than β carotene and ten times stronger than vitamin E. The largest source of lycopene can be obtained from tomatoes^{11,12}. Lycopene can inhibit several major growth signals, including Insulin Growth Factor (IGF) signals, vascular endothelial growth factor (VEGF) signals and platelet-derived growth factor (PDGF) signals that directly and/or indirectly result in decreased cell growth by inducing apoptosis and inhibiting the occurrence of angiogenesis.

The objective of this study was to prove the effect of the combination of dutasteride and lycopene in reducing the rate of bleeding complications at TURP evaluated by VEGF expressions and hemoglobin levels.

MATERIALS AND METHODS

Study design and location: The study is an experimental double blind randomized control trial post test only. It was performed by comparing changes in angiogenesis with VEGF expression and hemoglobin levels as the parameter. The study was carried out in Urology Department of Dr. Riadi Hospital Semarang from November, 2017 to March, 2018.

Sampling method: The target population was BPH patients who will undergo TURP surgery. The affordable population was the patients who were clinically and sonographically diagnosed as BPH who came to the urology clinic, emergency room and urology inpatient ward in Dr. Kariadi Hospital Semarang.

The sample in this study was divided into 2 groups by random allocation:

- Group 1 (C) was taken from all males suffered from BPH who came to urology clinic, emergency room and urology inpatient ward in Dr. Kariadi Hospital Semarang, who were clinically and sonographically diagnosed as BPH and given dutasteride 0.5 mg once daily for at least 30 days prior to TURP surgery (control group)
- Group 2 (T) was taken from all males suffered from BPH who came to the urology clinic, emergency room and urology inpatient ward in Dr. Kariadi Hospital Semarang, who were clinically and sonographically diagnosed as BPH and given dutasteride therapy 0.5 mg once daily and lycopene capsules 30 mg once daily for at least 30 days prior to TURP surgery (treatment group)

Data collection: Both groups take the medicine for at least 30 days prior to surgery. If the TURP procedure cannot be performed on the 30th day, the drug will continue to be given until the procedure is carried out. Blood was taken and blood laboratory tests were carried out for no more than 24 h following the surgery. TURP procedure was performed and recorded for the operation date and duration of surgery. Hemoglobin level post TURP was evaluated in the ward within a maximum of 2 h after TURP procedure. The prostate tissue was taken as much as 5-10 periurethra prostate scrapings placed in a plastic specimen container containing formaldehyde and then delivered to the Pathology Anatomy Laboratory of Diponegoro University Medical Faculty Semarang for immunohistochemical examination in order to assess the expression of VEGF after treatment.

In this study, the difference of VEGF expression and Hb levels pre and post TURP surgery can be seen. The first variable in this study was VEGF expression performed by histopathological examination and tested using immunohistochemical (IHC) techniques and a ratio measuring scale. The second variable was the hemoglobin level during pre and post TURP surgery taken from median cubital vein samples and examined using an hemoglobin analyzer and a ratio measuring scale.

This study was conducted on 22 BPH patients with urinary retention who underwent TURP procedure and met the inclusion and exclusion criteria. During the study period, 2 subjects dropped out of the study; 1 subject did not want to be operated (C group) and 1 subject dropped out because of the results of the Pathology Anatomy examination was malignancy of the prostate (T group) so that subjects who qualified to continue the study were only 20 subjects.

Ethical considerations: The study started when ethical clearance was given by the Ethical Committee of Research in Universitas Diponegoro Medical Faculty/Dr. Kariadi Hospital Semarang. Informed consent was given to each participant following a detailed explanation about the aim of the study and effect of the approaches.

Statistical analysis: All data scales were in ratio and there were two variables analysed; VEGF expression and hemoglobin levels. Normal distribution of data was obtained. Therefore, the analysis carried out was a t-test.

RESULTS

VEGF expression was evaluated on both groups. Statistical analysis used was independent t test. The result was $p = 0.430$ which means there isn't any significant difference between

Table 1: VEGF differences between the control and treatment groups

Variable	Group		p-value
	Control	Treatment	
VEGF expression	1.73 ± 0.62	1.91 ± 0.33	0.43 [§]

[§]Independent t

Table 2: Average data of hemoglobin level between pre and post TURP

Hemoglobin	Group		p-value
	Control	Treatment	
Pre test	14.27 ± 1.75	12.96 ± 1.76	0.11 [§]
Post test	13.45 ± 1.81	12.73 ± 1.60	0.36 [§]
p-value	<0.00 ^{*,*}	0.04 ^{*,*}	

Significant $p < 0.05$, [§]Independent t, ^{}Paired t test

Table 3: Average data of Δ Hemoglobin level in each group

Groups	Δ Hemoglobin level (Mean ± SD)	p-value
C	-0.82 ± 0.48	0.00 ^{*,*}
T	-0.23 ± 0.31	

Significant $p < 0.05$, ^{}Mann whitney, Δ Hb is subtraction of post surgery hemoglobin levels and pre surgery hemoglobin levels

the control and the treatment group regarding the VEGF expression difference (Table 1).

The results of the independent t-test in the C group of pre-examination hemoglobin levels showed a mean of 14.27 with a standard deviation of ± 1.75 and in the post examination the mean was 13.45 with a standard deviation of ± 1.81 . In the T group, the pre-examination hemoglobin level showed a mean of 12.96 with standard deviation of ± 1.76 and in the post examination the mean was 12.73 with a standard deviation of ± 1.60 . Obtained differences in preoperative hemoglobin levels between groups $p = 0.11$ so there was no significant difference. The difference in postoperative hemoglobin levels between groups $p = 0.36$ showed that there was no significant differences in the same test. The results of paired t-test with Hb levels in pre and postoperative state for each group showed the results of $p = < 0.001$ in group C and $p = 0.043$ in group T. This showed a significant difference (Table 2).

In the statistical test with the independent t-test in 2 groups, the $p = 0.00$ which means that the difference in the decrease in hemoglobin levels in pre and postoperative state for the 2 groups was significant (Table 3).

DISCUSSION

Angiogenesis affects the development of BPH, therefore anti-therapy angiogenics will work directly on the endothelial barrier vascular by inhibiting the production and action of pro angiogenic peptides from tumor cells and also strengthening the expression of angiogenesis inhibitors in tumors. Some of

the mechanisms of the 5 α reductase inhibitor have been mentioned, among others, reduction of androgen dependent angiogenic growth factors, such as vascular endothelial growth factor (VEGF), reduction of sub urothelial microvessel density and decreased blood vessels flow causing the prostate gland to shrink and induces apoptosis⁴. Angiogenesis will facilitate cell growth tumor by providing oxygenation to the tumor through various stages, including endothelial cell proliferation, capillary differentiation and motility of cells endothelial through the extracellular matrix so that stimulation will occur angiogenic. Depressed angiogenesis will reduce bleeding after transurethral resection of the prostate (TURP) surgery¹³.

In the study, it was found that lycopene can inhibit several major growth signals, including insulin growth factor (IGF) signals, VEGF signals and platelet-derived growth factor (PDGF) signals that directly and/or indirectly result in decreased cell growth by inducing apoptosis and inhibiting the occurrence of angiogenesis. Lycopene can reduce 5 α reductase inhibitors type 2 which is an enzyme responsible for converting testosterone into an active ligand for the androgen receptor. Another study found that lycopene administration at a dose of 15 mg/day for 6 months can inhibit disease progression and improve symptoms in BPH patients in which the same effect is also found in dutasteride and finasteride, where the drugs target the 5 α reductase inhibitor enzyme type 2 to be inhibited⁷. It can be concluded that dutasteride and *Solanum lycopersium* 30 mg have interconnected effects in terms of inhibiting angiogenesis factors. The two agents will together reduce the activity of VEGF, which will inhibit growth of capillary endothelial cell, so the angiogenesis and prostate vascularization will decrease. The use of finasteride in 2-4 weeks preoperatively can reduce total blood loss, blood loss per gram of resected prostate tissue, changes in hemoglobin level, microvascular density (MVD) and VEGF. In this study, VEGF expression obtained $p = 0.43$ with $p > 0.05$. These results indicate that giving a combination of dutasteride and lycopene for at least 30 days during pre TURP procedure which can reduce VEGF levels after TURP procedure was not significant compared to dutasteride alone.

Research conducted by administering dutasteride was not meaningful for reduced levels of MVD and VEGF on the prostate as the result of this study was not significant⁶. In that study, the effect to reduce the rate of bleeding complications in BPH is reducing the size of the prostate gland and increasing the stability of the blood vessel wall, compared to only decreasing vascularization⁸. In that research reported, finasteride will reduce the amount of bleeding and MVD

during TURP. It was found that administration of finasteride before doing TURP will decrease the hemoglobin more minimal and patient does not require transfusion compared to the control group (without 0 finasteride)⁹.

Complication that often occurs during TURP and post-surgery is bleeding which will lead to the increase of the morbidity and mortality rates. Some studies have reported that the number of blood needs during TURP surgery varies between 1-10%². Pastore *et al.*¹⁴ mentioned that pretreatment using dutasteride for 6 weeks before TURP procedure could significantly reduce surgical bleeding. Study of Kim *et al.*¹⁵ indicated that preoperative treatment with dutasteride for 2 weeks before TURP reduced surgical bleeding and length of stay after TURP. In this study there was a significant decrease in hemoglobin levels in the treatment group. The second hypothesis test found $p = 0.004$ with $p < 0.05$. These results showed that the decrease in the amount of bleeding in the group administered with the combination of dutasteride and lycopene (group T) was smaller than the group administered with dutasteride singly (group C). In another study it was found that pre-treatment surgery with dutasteride for 2 weeks before TURP reduced surgical bleeding and length of stay after TURP. It was found that group T showed a significant difference in the rate of reduction in Hb levels compared to group C. In this case, the minor hypothesis of the study proved that the combination of dutasteride and lycopene was stronger in suppressing the decrease in Hb.

The use of dutasteride combined with lycopene prior to TURP surgery in BPH patients should be considered in the future for reducing the post surgery bleeding. It would be better if the duration of treatment prior to TURP procedure can be extended to more than 30 days, larger samples would also be beneficial.

CONCLUSION

Combination of Dutasteride and lycopene 30 days prior to TURP surgery is not significant compared to Dutasteride alone in decreasing VEGF expression. The combination of dutasteride and lycopene once daily 30 days prior to TURP surgery significantly reduce blood loss showed by hemoglobin levels pre and post operative.

SIGNIFICANCE STATEMENT

This study discovers the possible benefit of dutasteride combined with lycopene in controlling the bleeding of post TURP surgery in BPH patients. It is known that dutasteride and

lycopene can inhibit angiogenesis process, thus bleeding they can be used to reduce bleeding, intraoperative and the need of blood transfusion post surgery. Effect of dutasteride and lycopene combination on BPH patients is reduced VEGF expressions and less hemoglobin decrease post surgery. This study will help the researcher to uncover the theory. Thus, a new implication of the drugs combination can be further considered.

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