THE EFFICACY OF DUTASTERIDE AND GREEN TEA TOWARDS BLEEDING ON BPH AFTER TURP: STUDY THEIR EFFECT ON HIF-1α EXPRESSION & HEMATOCRIT

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ABSTRACT

Objective: *This study proves differentiation of the combination of dutasteride and green tea, dutasteride, green tea, and placebo alone and their association with differences in hematocrit levels and the expression of hypoxia induced factor-1 alpha (HIF-1α) in patients with Benign Prostate Hyperplasia (BPH) were performed Trans urethral resection of the prostate (TURP) surgery.* ***Material & method:*** *Experimental study with the draft "randomized control trial". Comparing angiogenesis changes between groups of BPH patients who underwent TURP surgery to assess the expression of HIF-1α and Δ Ht (Hematocrit) after administration of dutasteride, green tea with combination of dutasteride and green tea for 14 days.* ***Results:*** *The combination of dutasteride and green tea was not significant in reducing the expression of HIF-1α. Mean P1 group (59.32 ± 14.69); P2 group (59.11 ± 20.73); P3 group (64.21 ± 14.95); K group (58.16 ± 16.00). Kruskal test results obtained p=0.491 walis which means the difference percentage of HIF-1α among the 4 groups was not significant. The mean Δ Ht P1 group (0.61 ± 0.204); P2 group (0.54 ± 0.250); P3 group (0.41 ± 0.275); group K (0.41 ± 0.275). In statistical test with Mann Whitney test comparing the percentage reduction obtained Ht levels dutasteride group against group of green tea obtained p=0.213 means that there is no significant difference. Where a significant difference to the other groups.* ***Conclusion:*** *The combination of dutasteride and green tea for 14 days before TURP surgery does not reduce the expression of HIF-1α in BPH patients who underwent TURP surgery. Δ Ht significant decline in the combination group compared with other groups and might be influenced by several factors during TURP surgery.*

Keywords: *HIF-1α, hematocrit, benign prostate hyperplasia, dutasteride, green tea.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan membuktikan perbedaan kadar hematokrit dan ekspresi hypoxia induced factor-1 alpha (HIF-1α) antara kombinasi dutasteride dan teh hijau, dutasteride, teh hijau, dan placebo tunggal pada pasien Benign Prostate Hyperplasia (BPH) yang dilakukan operasi Trans urethral resection of the prostate (TURP).* ***Bahan & cara****: Studi eksperimental dengan rancangan "randomized control trial". Membandingkan perubahan angiogenesis antara kelompok pasien BPH yang menjalani operasi TURP terhadap ekspresi HIF-1α dan Δ Ht (Hematocrit) setelah pemberian dutasteride, teh hijau dan kombinasi dutasteride dan teh hijau selama 14 hari.* ***Hasil:*** *Kombinasi dutasteride dan teh hijau tidak bermakna dalam menurunkan ekspresi HIF-1α. Rerata kelompok P1 (59.32 ± 14.69); kelompok P2 (59.11 ± 20.73); kelompok P3 (64.21 ± 14.95); kelompok K (58.16 ± 16.00). uji Kruskal-walis diperoleh p=0.491 dimana perbedaan persentase diantara 4 kelompok tidak bermakna. Rerata Δ Ht kelompok P1 (0.61 ± 0.204); kelompok P2 (0.54 ± 0.250); kelompok P3 (0.41 ± 0.275); kelompok K (0.41 ± 0.275). Uji statistika Mann-Whitney membandingkan persentase penurunan kadar Ht kelompok dutasteride terhadap kelompok teh hijau diperoleh p=0.213 sehingga tidak ada perbedaan bermakna, dimana ada perbedaan yang bermakna terhadap kelompok lainnya.* ***Simpulan:*** *Kombinasi dutasteride dan teh hijau selama 14 hari sebelum operasi TURP tidak menurunkan ekspresi HIF-1α pada pasien BPH yang menjalani operasi TURP. Penurunan Δ Ht yang bermakna pada kelompok kombinasi dibandingkan dengan kelompok lain mungkin dipengaruhi oleh beberapa faktor pada saat operasi TURP.*

Kata kunci: *HIF-1α, hematocrit, benign prostate hyperplasia, dutasteride, teh hijau.*

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INTRODUCTION

Benign Prostate Hyperplasia (BPH) or benign enlargement of the prostate gland is often found in elderly. Clinical symptoms arise due to BPH interfered daily activities. In 2025, an estimated 5 million to 9 million people will have BPH. BPH is the second most common disease in urology clinic in Indonesia.[1]

The cause of BPH is unknown for certain, but currently it associated with decreased levels of male hormones caused by the aging process, especially testosterone. Testosterone in the prostate gland will be converted into dehidrotestosteron (DHT). The prostate gland will be enlarged due to chronically stimulated by DHT.[2]

Various kinds of therapy in patients with BPH both medical and surgical.[3] Trans urethral resection of the prostate (TURP) is one of the most often performed.[4] Bleeding complications often occur in both during TURP or postoperative could increase morbidity and mortality. Research in 1987 at Dr Kariadi Hospital obtained hemoglobin levels decreased between 0.4–1.8 g, in 1992 earned decreased hemoglobin levels between 0.4–2.6 g.[5,6] Possibility cloth retention and hematuria occurs after TURP operation.[7,8]

The process of angiogenesis occurs in BPH, which will get an increase in blood vessel cross-sectional area and density of the number of blood vessels per field of view on prostate specimens that facilitate the emergence of bleeding during TURP action. The amount of bleeding that occurs during operation depends on the duration of use of catheter, prostate volume, operator skills, operation length, and the presence of comorbid factors such as diabetes mellitus and hypertension.[9] Some of the research being conducted to find factors inhibiting angiogenesis (anti-angiogenic), one of which therapy is 5-α reductase inhibitors, There are two kinds of agent α reductase inhibitors 5, there are dutasteride and finasteride. Principles of drug action is the inhibition of the conversion of testosterone to 5α dehidrotestosterone (DHT), which causes enlargement of prostat.[10,11] The agent can reduce the expression of hypoxia induced factor-1 alpha (HIF-1α) and vascular endothelial growth factor (VEGF) in the sub-epithelial prostate tissue.[12]

Research in 2004, found that dutasteride make DHT levels get low when compared with finasteride.[13] Therefore, in previous studies of dutasteride effect on decreasing DHT levels better than finasteride so that the drug is selected to be used for this research.

Green tea is one of the other therapies to suppress angiogenesis. Inside the green tea, we can found one type of component epigallocatechin gallate (EGCG), which proved to prevent the growth of blood vessels in experimental animals. EGCG concentration sufficiently effective in green tea drinkers. EGCG inhibits urokinase and activation of tyrosine kinases, which serves as an activator of growth factors such as VEGF, EGF, and FGF.[14] prostate tumor therapy with EGCG with iron ions eliminate transcription-mediated enhancement of HIF-1α.[15]

OBJECTIVE

Based on the existing literature, the researcher wanted to test the effect of green tea and dutasteride synergism in terms of inhibiting angiogenesis.

MATERIAL & METHOD

This study is an experimental study with randomized controled trial design. Patients were clinically and sonography has been diagnosed as BPH who came to urology clinic, emergency surgery, and urology hospital inpatient ward of Dr. Kariadi to be performed TURP. The sample in this study were divided into 4 groups randomly allocated: 1). Group 1 (P1) Provision 0.5mg dutasteride therapy (once per day); 2). Group 2 (P2) Provision of green tea 1 capsule therapy (once per day); 3). Group 3 (P3) Provision of a combination therapy of dutasteride 0.5mg and 1 green tea capsules (once per day); 4). Group 4 (K) Provision placebo (once per day). Each drugs are administered for at least 14 days prior to undergoing TURP surgery. Then each sample filling out the form following the approval of research.

TURP specimens taken by 5-10 scrapings periurethra prostate and sent to the lab PA then examined the expression of HIF-1α (hypoxia induced factor-1 alpha) with a paraffin block technique using monoclonal antibodies Rabbit HIF-1α (Bioss). Examination using immunohisto-chemical techniques.

For hematocrit examination and investigation in preparation for surgery, blood samples were taken from the median cubital vein. A total of 3cc of blood put into EDTA tubes by using

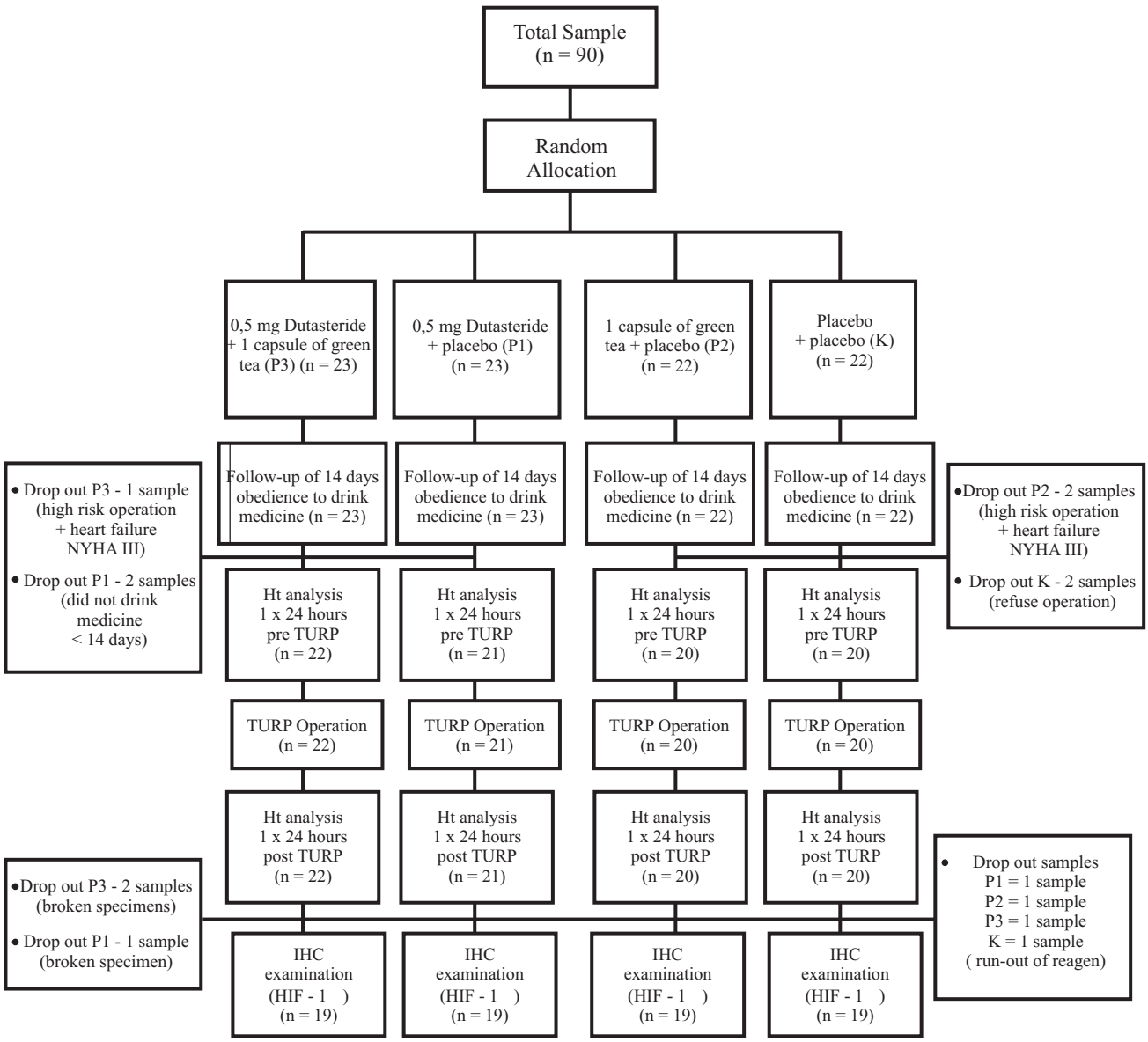
hemoglobin analyzer brands Symex (before and after TURP surgery).

Research and data collection carried out for 6 months (July 2012 until May 2013). Treatment of samples performed in Installing the Central Surgical of Dr Kariadi hospital. The process of examining the levels of HIF-1α carried out in the Laboratory of Pathology Anatomy and hematocrit in Clinical Pathology Laboratory at Medical Faculty Diponegoro University, Semarang.

Data from the research that has been recorded, collected, and processed with SPSS v.15.

RESULTS

All BPH patients who met the inclusion criteria noted identity, body temperature, the results of routine blood tests, urine routine, blood chemistry (liver and kidney function), PSA, urine culture, transrectal prostate volume. After receiving



Picture 1. Consolidated research report.

Table 1. Data characteristic on TURP surgery.

Description	Group P1 (Dutasteride+placebo)	Group P2 (Teh hijau + placebo)	Group P3 (Dutasteride+Teh hijau)	Group K (Placebo+placebo)	p
n	19	19	19	19	
Age (Mean, SD)	67.74 ± 7.76	70.26 ± 9.50	70.37 ± 6.80	70.42 ± 8.87	0.703
Prostate volume (cc)	45.63 ± 17.46	43.1 ± 14.84	39.63 ± 13.24	44.09 ± 17.61	0.693
Operation length (minute)	35.37 ± 2.81	35.00 ± 3.05	34.32 ± 4.07	34.58 ± 3.59	0.789
Length of drugs consumption (days)	14.63 ± 0.895	14.68 ± 1.057	14.74 ± 0.933	14.84 ± 1.167	0.957
Ht before TURP (%)	37.61 ± 1.76	37.06 ± 1.52	37.20 ± 1.66	37.78 ± 2.06	0.559

treatment with the drug was given for at least 14 days, 1 x 24 hour before operation patients examined hematocrit, and blood clotting factors were normal and the patient performed the procedure TURP (Trans Urethral Resection of the Prostate), note the date of the operation and the number of scrapings prostate tissue specimen TURP prostate scrapings taken by 5-10 periurethra and sent to the lab PA then examined HIF-1α with a paraffin block technique. After operation Ht levels 1 x 24 hour examined, and expression of HIF-1α. During the period of 14 days or more there is no group that drank other types of tea, taking anticoagulants and there were 14 samples that drop out.

Results of data characteristics table (Table 1) conducted by one way ANOVA statistical test because the data obtained in the normal distribution and homogeneous for age between groups was obtained p=0.703 which means that the difference is not significant. Prostate volume between groups was obtained p=0.693 which means the difference was not significant and the operating time between groups was obtained p=0.789 which means the difference was not significant.

The results of the statistical test Kruskal Wallis test in 4 groups obtained p=0.491 which means the percentage difference of HIF-1α among the 4 groups was not significant (Table 2).

Table 2. The mean percentage of HIF-1α (%) in each group.

Percentage of HIF-1 (%)	Mean	SD	p
P1	59.32	14.69	0.491‡
P2	59.11	20.73	
P3	64.21	14.95	
K	58.16	16.00	

Specification :
* Significant p<0.05 ‡ Kruskal Wallis test

The results of the Kruskal Wallis test in 4 groups obtained p=0.000 which means that the difference decreased levels of before and after operation hematocrit in 4 groups is significant. But to know which groups are significant then followed by Mann Whitney test (table 3).

Table 3. The mean Δ HT concentration (%) in each group.

Treatment	Mean	SD	p
P1	-0.61	0.20	0.000*‡
P2	-0.54	0.25	
P3	-0.41	0.27	
K	-1.13	0.69	

Specification :
* Significant p<0.05 ‡ Kruskal Wallis test

Statistical test results obtained with Mann Whitney test comparing the percentage reduction in hematocrit levels of the group P1 to P2 group obtained p=0.213 means that there is no significant difference. group P1 to P3 group obtained p=0.001 means that there is a significant difference. P1 group against group K was obtained p=0.005 means that there is a significant difference. group P2 to P3 group obtained p=0.005 means that there is a significant difference. P2 group against group K was obtained p=0.001 means that there is a significant difference. P3 group against group K was obtained p=0.000 means that there are significant differences (table 4).

Table 4. Significance levels Δ Ht (%) among each group.

Δ Ht level (%)£	P2	P3	K
P1	0.213	0.001*	0.005*
P2	–	0.005*	0.001*
P3		–	0.000*

Specification :
* Significant p<0.05 £ Mann Whitney test

DISCUSSION

Statistical analysis showed that there was no significant difference in the percentage of HIF-1α between the group given the combination of dutasteride and green tea (P3) with a group who were given dutasteride alone (P1), the group given only green tea (P2) and the untreated group (K).

Past research suggests that 5α reductase inhibitor agent (dutasteride) can reduce the expression of HIF-1α in the sub-epithelial prostate tissue.[12] Prostate tumor therapy with EGCG which is the active compound of green tea with iron ions eliminate transcription-mediated increase in HIF-1α that appear on monotherapy with EGCG.[15] It is expected that work occurred synergism between green tea with dutasteride.

Theoretically hypoxia is suspected as the most potent stimulator of VEGF, and its expression is regulated by HIF transcriptional-1. Role of HIF-1 is very important, as a regulator of transcription of the genome is widely identified for hemostasis O2 in response to hypoxic stress. HIF-1 is a heterodimer consisting of a subunit of HIF-1α and HIF-1β. HIF-1β are constitutively expressed, where the expression of HIF-1α is maintained at low levels in most cells under normal condition.[16]

In hypoxic conditions, HIF-1α release proteosomal degradation and then translocated to the nucleus. Processes that formed as a result of inhibition of the activity of the oxygen-dependent prolylhidroxylase modify residues 564 and 402, and the next process is mediated by signal-cell nucleus localization signal. This enzymatic modification of HIF-1α is required for protein binding of von Hippellindau, which identify the components of the ubiquitin protein ligase E3 which is the target of HIF-1α for proteosomal degradation. In contrast to the arrangement of oxygen dependence of the degradation of HIF-1α, reported factors that induce the synthesis of protein HIF-1α through the signal transduction pathway leads to receptor tyrosine kinases of the PI3K to the serine/threonine kinase AKT and FRAP.[16,17]

In this study we found there is no significant difference in the percentage of the group with a combination of dutasteride and green tea compared with the three other groups. Group who were given green tea (P2) is expected to occur inhibitory pathways P13K/Akt by green tea resulted in the production of HIF-1α will decrease so that angiogenesis may be correspondingly reduced. However, this result is not as expected, according to research conducted by Hilpakka RA et al, that the EGCG in green tea may have potential for inhibiting the activity of 5α-reductase that influence BPH.[18] Liao S et al, found that the content of EGCG in green tea work synergism in strengthening the inhibitory effects of 5α-reductase by dutasteride.[19] It can be concluded that if the work itself becomes less effective green tea.

Just giving dutasteride group alone (P1) compared with the three other groups no significant difference. Dutasteride works by lowering the activity of growth factor inhibits the conversion of testosterone into dehidrotestosteron (DHT), making androgen activity decreased thereby decreasing the activation of tyrosine kinases and reduce the production of HIF-1α. According to research conducted by Pastore et al, and Kravchick et al, that after 6 weeks of giving new dutasteride can reduce prostate tissue vascularization. Research conducted by Ku JH et al, that the administration of dutasteride less than 4 weeks are not suppress the expression of HIF-1α in human prostate tissue. Maybe the causes of no significant results from differences percentages in the expression of HIF-1α between that groups.[12,20,21] Length time administration can also affect the effectiveness of the drug.

Administration of a combination of dutasteride group and green tea (P3) with three other groups the percentage difference expression of HIF-1α was not significant. In bioavailability, the green tea polyphenols easily absorbed on empty stomach by the mucose intestine. The absorbtion greatly influenced by pH, the food in the intestine, alcohol, cigarettes, an enzyme involved in bile in metabolisme.[22] these factors that cause inter-individual pharmacokinetic variability of conjugate and non-conjugate form green tea polyphenols in blood plasma.[22] maximum levels of green tea polyphenols in blood plasma reached 2-4 hours after ingestion. Maximum EGCG plasma concentration is achieved after 4 hours and the slowest down with t1/2 almost 7 hour.[22,23] Therefore allegedly non-significant results is affected by the variability in the pharmacokinetics of green tea polyphenols and duration of dutasteride consumption were less than 4 week.

Other factors can affect the results significantly to the expression of HIF-1α is a JAK/STAT 3 pathway. Research conducted Matsumura et al, found that the expression of HIF-1α not only affected by hypoxic conditions, but also can be increased

regulation by the JAK/STAT 3 pathway, where the line was not yet known whether affected by green tea and dutasteride or not.[24]

The results of the statistical test of differences before and after operation hematocrit levels between groups was found in the combination of dutasteride group and green tea (P3) is slightly decreased when compared with the group given only dutasteride alone (P1), and green tea (P2) or without treatment (K) significantly with $p<0.05$. Differences between groups P2 hematocrit reduction the K group significantly, but with no significant group P1. Between group P1 with group K there is a difference significant decrease in hematocrit levels.

TURP is still the gold standard for the treatment of BPH cases. The most common complications are bleeding and perioperative intra. However, the bleeding is expected to be reduced by administration of green tea and dutasteride. The results have not been as expected that the group given the combination of green tea and dutasteride more potent in reducing the expression of HIF-1 in line with reducing pre and post-TURP bleeding when compared to administration of dutasteride or green tea alone or without given both drugs.

The results of the statistical test of differences in levels of pre and postoperative hematocrit levels between groups was found in the combination of dutasteride group and green tea (P3) is slightly decreased when compared with the group given only dutasteride alone (P1), and green tea (P2) or without treatment (K) significantly, differences between groups in hematocrit decrease in P2 with significant K groups, the group P1 with group K there is a difference significant decrease in hematocrit levels. There are several factors that can affect hematocrit decrease in postoperative TURP in this study, among others, long action and fluid balance. Research conducted by Ather et al, found that the bleeding that occurs at the time of TURP is influenced by the operating time and size prostat.[25] Research conducted by Kirollos et al, also suggest that the size of the prostate affect bleeding during surgery TURP.[26] Research conducted by Miyao H et al, found that there are differences in hematocrit in the group who had TURP syndrome with asymptomatic. The decrease in hematocrit is assumed to occur because of hemodilution during TURP surgery which is also influenced by the operation length time.[27]

The result of statistical test between the groups given only dutasteride alone (P1) with a given group of green tea (P2) is not significant in hemotocrite level decreases. Research conducted Pastore et al, found a decrease in hemoglobin or hematocrit significantly to the provision of dutasteride for 6 weeks.[21] However, the research conducted by Hahn RG et al, not found any significant difference in blood loss between the groups given dutasteride with the group without treatment.[28] Results of research conducted by Boccon-Gilbod L et al, concluded that the difference in blood loss in patients given previous dutasteride for 4 weeks compared with the untreated group after TURP showed no significant results. Nonsignificant results are assumed to occur by being influenced by the length of therapy that affects the decrease in hematocrit at TURP surgery.[29]

CONCLUSION

The combination of dutasteride and green tea for 14 days before TURP surgery does not reduce the expression of HIF-1α in BPH patients who underwent TURP surgery. ΔHt significant decline in the combination group compared with other groups and might be influenced by several factors during TURP surgery.

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