The Effect of Dutaseride and Tomato Extract Combination on Reducing Blood Loss after Transurethral Resection of the Prostate

by Eriawan Agung Nugroho

Submission date: 11-Mar-2022 08:55AM (UTC+0700)
Submission ID: 1781544563
File name: artikel.pdf (552.16K)
Word count: 3070
Character count: 16756

Urological Science

Journal homepage:www.e-urol-sci.com

Original Article

The Effect of Dutasteride and Tomato Extract Combination on Reducing Blood Loss after Transurethral Resection of the Prostate

Eriawan Agung Nugroho[1]*, Selly Adyta Kemara[2], Siti Amarwati[3], Tommy Supit[2]

Departments of [1]Urology, [2]General Surgery and [3]Anatomy Pathology, Faculty of Medicine, Diponegoro University, Dr. Kariadi General Hospital, Semarang, Indonesia

Abstract

Context: Lycopene, a carotenoid found in tomatoes, possesses antiangiogenic activities that might be useful in the management of prostate enlargement. However, the current evidence is still inconclusive in regard to this matter. **Aims:** The aim of the study was to investigate the effect of combined oral dutasteride and lycopene consumption in reducing posttransurethral resection of the prostate (TURP) bleeding. **Settings and Design:** Twenty-two individuals diagnosed with benign prostatic hyperplasia were randomly allocated into two groups of equal size. Thirty days prior to TURP, individuals in Group 1 (control) were given daily oral dutasteride 0.5 mg and placebo pill and individuals in Group 2 (intervention) were given dutasteride 0.5 mg and lycopene 30 mg. **Subjects and Methods:** The parameters measured in this study were pre- and post-TURP plasma erythrocyte count and microvessel density (MVD) of resected prostate tissue stained with CD34. **Statistical Analysis Used:** Data homogeneity was tested using the Shapiro–Wilk test. Individuals' characteristics were analyzed using the Mann–Whitney U-test and plasma erythrocyte and MVD analyzed using the *t*-test. Spearman's correlation analysis was performed to find significant correlations between the two variables. **Results:** There were two dropouts. The mean MVD in the control group was significantly higher compared to the intervention group (28.2 ± 12.3 vs. 18.3 ± 7.6 vessel/mm^2, $P = 0.044$). Reduction of post-TURP plasma erythrocytes was significantly higher in the control group compared to the intervention group (-0.34 ± 0.18 vs. -0.17 ± 0.12 $10^6/\mu L$, $P = 0.048$). **Conclusions:** Daily consumption of dutasteride and lycopene for at least 30 days reduced the formation of blood vessels in the prostate and reduced blood loss post-TURP.

Keywords: Angiogenesis, bleeding, dutasteride, lycopene, *Solanum lycopersicum,* tomato extract, transurethral resection of the prostate

Introduction

Transurethral resection of the prostate (TURP) remains a gold standard in the treatment of benign prostatic hyperplasia (BPH) and is frequently performed in our institution.[1,2] Albeit low in incidence, postoperative hemorrhage after TURP remains a potentially life-threatening complication that requires a prompt blood transfusion.[3] Dutasteride is a 5-α-reductase inhibitor (5-ARI) proven effective in reducing prostate volume by inhibiting the synthesis of dihydrotestosterone.[4] The drug also decreases prostatic vascularity by means of inhibiting vascular endothelial growth factor (VEGF) expression,

Received: 31-Dec-2018 **Revised:** 08-Apr-2019 **Accepted:** 30-Apr-2019

Access this article online

Quick Response Code:

Website: www.e-urol-sci.com

DOI: 10.4103/UROS.UROS_152_18

Address for correspondence: Dr. Eriawan Agung Nugroho, Jl. Dr. Sutomo No. 16, Randusari, Semarang 50244, Indonesia. E-mail: eriawanspu@gmail.com

How to cite this article: Nugroho EA, Kemara SA, Amarwati S, Supit T. The effect of dutasteride and tomato extract combination on reducing blood loss after transurethral resection of the prostate. Urol Sci 2019;30:216-9.

reducing vascular density within the prostatic suburethral tissue.[5,6] This translates its use as a treatment of BPH for reducing blood loss. Preoperative treatment with dutasteride for 2 weeks prior to TURP was shown to reduce surgical bleeding and length of hospitalization.[7,8]

Lycopene, a carotenoid found in tomatoes, is one of the best research phytotherapeutic agents for prostate cancer. Initial investigations of its effect on prostate cancer led to an observation of a protective effect on BPH, where a high intake of lycopene was associated with reduced risk of BPH.[9] The beneficial effect was hypothesized to be a result of a multitude of biochemical effects of the carotenoid; antioxidative, anti-inflammatory, proapoptotic, and antiproliferative.[10-12] Lycopene was also found to possess antiangiogenesis activity, similar to dutasteride.[13] A further molecular study demonstrated that such effect was a result of the inhibition of VEGF receptor-2 (VEGFR2)-mediated phosphorylation of extracellular signal-regulated kinase (ERK)/p38 signaling pathways.[14] However, evidence of the reduction of vascularization within the prostatic tissue and the clinical outcome that results from it is lacking. This study investigated the effect of daily consumption of dutasteride and lycopene in patients with BPH prior to TURP, on prostate vascularity and perioperative bleeding.

Subjects and Methods

Patient selection

This clinical trial was performed in November 2017–March 2018 with ethical clearance from the governing board of ethics (707/EC/FK-RSDK/XII/2017). Twenty-two patients clinically diagnosed with the first case of acute urinary retention caused by BPH into two groups: group 1 (n = 11) comprised controls that received oral dutasteride (Avodart®, GlaxoSmithKline, Brentford, England) 0.5 mg/day and one capsule of placebo (sugar) and Group 2 (n = 11) intervention participants received daily dutasteride 0.5 mg/day and tomato extract (*Solanum lycopersicum*) lycopene (GNC, Indonesia). The pretreatment was given for at least 30 days prior to TURP. All drugs (dutasteride, lycopene, and placebo) were each prepared into a plain 00-size red gelatin capsule (Capsulcn International Co., Ltd., China) to ensure participant blinding. Two of each corresponding capsule were prepared in a clear plastic container labeled day 1 to day 30 to ease drug consumption. Each participant was supplied with a 15-day worth of treatment before required to return to the clinic for follow-up and top-up for the rest of 15 days. Those who failed to return a complete set of plastic container during follow-up were considered to be noncompliant and excluded from the study. Patients with renal failure, major cardiovascular disease, evidence of other genitourinary diseases, very large prostate (>90 mL), history of previous prostate surgery, and treatment with 5-ARI within 6 months were excluded.

One-blinded board-certified urologist measured the initial prostate volume using transrectal ultrasound (TRUS) with ellipsoid formula and performed all the TURP. Prostate resection was performed using bipolar 24-Fr resectoscope (Karl Storz®, Tuttlingen, Germany) under spinal anesthesia with sterile water (Otsuka Pharmaceutical, Japan) as irrigation. Resected periurethral tissue was fixated in 10% neutral buffered formalin and paraffinized for further histopathological analysis. A postoperative 22-Fr three-way urinary catheter with continuous irrigation with sterile water was maintained for an additional 48 h unless bleeding was still observable.

Hematology and histopathological examination

The level of plasma erythrocytes (million cells/μL) was analyzed from 3 mL of blood taken from a median cubital vein 1 h before and after TURP. Blood samples were analyzed using Sysmex KX-21 Automated Hematology Analyzer (Sysmex, Shanghai, China). The difference of erythrocyte count was quantified from the subtraction of pre-TURP with the post-TURP value. Prostate angiogenesis was evaluated in terms of microvascular density (MVD) by immunohistochemistry.[15] Paraffin blocks of resected prostate tissue were processed for CD34 (DAKI M.7165) staining using the standard labeled streptavidin-biotin technique. Microscopic analysis was performed using Olympus BX41 light microscope (Olympus, Japan) at ×4 magnification to locate areas with the highest microvessel concentration. Quantification of MVD (vessel/mm^2) was made from 10 high-power views at ×100 magnification within the determined area of microvascular "hotspots." Histological confirmation of BPH diagnosis and MVD analysis was conducted blinded by one board-certified pathologist.

Statistical analysis

The Shapiro–Wilk test was used to determine the data normality. Individuals' characteristics were analyzed using the Mann–Whitney U-test and plasma erythrocyte and MVD analyzed using the t-test. Spearman's correlation analysis was performed to find significant correlations between the two variables. All statistical analysis was performed using SPSS (SPSS Inc., IBM Corporation, New York, USA). Data were presented in mean ± standard deviation unless stated otherwise. Statistical significance was set at $P < 0.05$.

Results

One patient dropped out from the intervention group because he did not consent for TURP operation. Histological analysis of the prostate tissue of another patient was revealed to be malignant, thus excluded from the study. A total of twenty patients were accounted at the end of the study. No side effects of negative drug interaction between dutasteride and lycopene were reported. Individuals from both the groups shared similar baseline characteristics with no statistically significant differences [Table 1]. Male individuals in the lycopene group were slightly older (65.70 ± 7.76 vs. 65.00 ± 6.32 years, P = 0.83), had smaller prostate (36.12 vs. 37.53 mL, P = 0.59), shorter duration of pretreatment (26.12 vs. 37.53 days, P = 0.59), and usage of urinary catheter (32 vs. 34 days, P = 0.35). The operative time taken was almost identical for both the groups.

The mean reduction of erythrocyte and amount of MVD of the control group was significantly greater compared to the lycopene group (−0.3 ± 0.2 vs. −0.17 ± 0.12 million cells/μL, $P = 0.05$, and 28.20 ± 12.33 vs. 18.30 ± 7.62, $P = 0.04$, respectively). Spearman's correlation test showed a medium positive correlation between the two variables [Table 2].

Discussion

Dihydrotestosterone (DHT) blocker or 5-ARI is an accepted medication for treating BPH and is commonly prescribed along with alpha-1 adrenergic receptor blocker as combination therapy. Early experimental and animal studies with finasteride showed a reduction of prostatic blood flow and vascular density.[16,17] This sparks considerable interests in the utilization of 5-ARI for pretreatment before TURP to reduce perioperative blood loss, although such practice is not generally accepted.[18] 5-ARI blocks the conversion of testosterone to DHT, reducing the bioactivity of androgen-controlled angiogenic growth factors such as VEGF. Dutasteride acts on all three isoforms of 5α-reductase providing greater suppression than finasteride. This theoretically should produce a greater effect than finasteride. However, one meta-analysis showed that pretreatment with finasteride reduces perioperative blood loss but inconclusive for dutasteride.[19] The exact reason why dutasteride was inferior compared to finasteride in reducing angiogenesis remains to be elucidated.

Numerous studies have investigated the effect of lycopene consumption for the prevention and treatment of BPH and prostate cancer. A meta-analysis of eight randomized controlled trials showed that lycopene consumption decreased prostate cancer diagnosis (relative risk [RR] = 0.95, 95% confidence interval [CI] = 0.63, 1.44), decreased BPH diagnosis (RR = 0.92, 95% CI = 0.66, 1.29), and significantly reduced prostate-specific antigen levels (Mean difference (MD) = −6.00, 95% CI = −8.92, −3.08).[20] Numerous biochemical effects of lycopene have been described, mainly from the bioactivity of lycopenoids, the main metabolic product of lycopene.[21] The main interest of this study is the antiangiogenesis of lycopene because it directly translates to the number of blood vessels within the prostate. Less vascularity within the prostatic tissue means that fewer blood vessels are transected during TURP, which results in less blood loss. This is observed in this study where patients with smaller MVD suffered from less reduction of erythrocyte level as a result from bleeding.

The mechanism by which lycopene inhibits angiogenesis has been explored by Chen *et al*. in an *ex vivo* study using human umbilical vein endothelial cells (HUVECs). Lycopene inhibits MMP-2/uPA system through VEGFR2-mediated PI3K-Akt and ERK/p38 signaling pathways leading to a reduction in migration, invasion, and tube formation of HUVECs.[14] Whether the reduction of prostate vascularity is a result of similar mechanisms or in some other way is currently unknown.

Several study limitations were identified. There was a minor variability of the period of pretreatment, up to 4 days, caused by hospital logistics and operation queue. The biological effect of dutasteride and lycopene consumption in such a short period of time should be negligible.[11] There is no group in the study that received no treatment at all, including 5-ARI. The observed value from this study could be a result of the variability of the effect of dutasteride. A larger randomized controlled trial is required to confirm the finding of this study.

Short-term daily consumption of 30-mg lycopene and 0.5-mg dutasteride was more effective compared to dutasteride alone in reducing prostate MVD and perioperative blood loss related to TURP in patients with BPH. Lycopene can be considered as a safe phytotherapeutic agent combined with 5-ARI in reducing perioperative bleeding of BPH patients undergoing TURP.

Table 1: Baseline characteristics

	Control (n=10)	Lycopene (n=10)	P
Age (years old)	65.00±6.52	65.70±7.76	0.83
Prostate volume (mL)*	37.53 (32.18-70.60)	36.12 (25.45-86.03)	0.59
Duration of pretreatment (day)	31.70±1.42	31.90±1.66	0.77
Duration of catheter use (day)*	34 (32-36)	32 (32-33)	0.35
Duration of TURP (min)*	20 (14-40)	20 (15-42)	0.07

*Data presented as mean (range). TURP: Transurethral resection of the prostate

Table 2: Difference of erythrocyte count and microvessel density

	Control (n=10)	Lycopene (n=10)	P
Erythrocyte count	−0.3±0.2	−0.17±0.12	0.05
MVD	28.20±12.33	18.30±7.62	0.04
Correlation between erythrocyte count and MVD*			0.03

Spearman's correlation test. *MVD: Microvessel density

Acknowledgments

We would like to thank all operating theater and laboratory personnel who aided us in the making of this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Teo JS, Lee YM, Ho HS. An update on transurethral surgery for benign prostatic obstruction. Asian J Urol 2017;4:195-8.
2. Berardinelli F, Hinh P, Wang R. Minimally invasive surgery in the management of benign prostatic hyperplasia. Minerva Urol Nefrol 2009;61:269-89.

3. Rassweiler J, Teber D, Kuntz R, Hofmann R. Complications of transurethral resection of the prostate (TURP) – Incidence, management, and prevention. Eur Urol 2006;50:969-79.
4. Page ST, Hirano L, Gilchriest J, Dighe M, Amory JK, Marck BT, *et al.* Dutasteride reduces prostate size and prostate specific antigen in older hypogonadal men with benign prostatic hyperplasia undergoing testosterone replacement therapy. J Urol 2011;186:191-7.
5. Kravchick S, Cytron S, Mamonov A, Peled R, Linov L. Effect of short-term dutasteride therapy on prostate vascularity in patients with benign prostatic hyperplasia: A pilot study. Urology 2009;73:1274-8.
6. Zaitsu M, Tonooka A, Mikami K, Hattori M, Takeshima Y, Uekusa T, *et al.* A dual 5α-reductase inhibitor dutasteride caused reductions in vascular density and area in benign prostatic hyperplasia. ISRN Urol 2013;2013:863489.
7. Kim KS, Jeong WS, Park SY, Kim YT, Moon HS. The effect of two weeks of treatment with dutasteride on bleeding after transurethral resection of the prostate. World J Mens Health 2015;33:14-9.
8. Gökçe Mİ, Kerimov S, Akıncı A, Hamidi N, Afandiyev F, Yaman Ö. Effect of dutasteride treatment on reducing blood loss and in perioperative period of open prostatectomy. Turk J Urol 2015;41:24-6.
9. Kristal AR, Arnold KB, Schenk JM, Neuhouser ML, Goodman P, Penson DF, *et al.* Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: Results from the prostate cancer prevention trial. Am J Epidemiol 2008;167:925-34.
10. Story EN, Kopec RE, Schwartz SJ, Harris GK. An update on the health effects of tomato lycopene. Annu Rev Food Sci Technol 2010;1:189-210.
11. Mein JR, Lian F, Wang XD. Biological activity of lycopene metabolites: Implications for cancer prevention. Nutr Rev 2008;66:667-83.
12. Heber D, Lu QY. Overview of mechanisms of action of lycopene. Exp Biol Med (Maywood) 2002;227:920-3.
13. Yang CM, Yen YT, Huang CS, Hu ML. Growth inhibitory efficacy of lycopene and β-carotene against androgen-independent prostate tumor cells xenografted in nude mice. Mol Nutr Food Res 2011;55:606-12.
14. Chen ML, Lin YH, Yang CM, Hu ML. Lycopene inhibits angiogenesis both *in vitro* and *in vivo* by inhibiting MMP-2/uPA system through VEGFR2-mediated PI3K-Akt and ERK/p38 signaling pathways. Mol Nutr Food Res 2012;56:889-99.
15. Svagzdys S, Lesauskaite V, Pavalkis D, Nedzelskiene I, Pranys D, Tamelis A. Microvessel density as new prognostic marker after radiotherapy in rectal cancer. BMC Cancer 2009;9:95.
16. Häggström S, Tørring N, Møller K, Jensen E, Lund L, Nielsen JE, *et al.* Effects of finasteride on vascular endothelial growth factor. Scand J Urol Nephrol 2002;36:182-7.
17. Pareek G, Shevchuk M, Armenakas NA, Vasovic L, Hochberg DA, Basillote JB, *et al.* The effect of finasteride on the expression of vascular endothelial growth factor and microvessel density: A possible mechanism for decreased prostatic bleeding in treated patients. J Urol 2003;169:20-3.
18. Donohue JF, Barber NJ. How do we investigate haematuria and what role has finasteride? BJU Int 2004;93:3-4.
19. Zhu YP, Dai B, Zhang HL, Shi GH, Ye DW. Impact of preoperative 5α-reductase inhibitors on perioperative blood loss in patients with benign prostatic hyperplasia: A meta-analysis of randomized controlled trials. BMC Urol 2015;15:47.
20. Ilic D, Misso M. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: A systematic review. Maturitas 2012;72:269-76.
21. Erdman JW Jr., Ford NA, Lindshield BL. Are the health attributes of lycopene related to its antioxidant function? Arch Biochem Biophys 2009;483:229-35.

The Effect of Dutaseride and Tomato Extract Combination on Reducing Blood Loss after Transurethral Resection of the Prostate

ORIGINALITY REPORT

13%	9%	11%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Altug Tuncel. "Effects of short-term dutasteride and Serenoa repens on perioperative bleeding and microvessel density in patients undergoing transurethral resection of the prostate", Scandinavian Journal of Urology and Nephrology, 2009 Publication	1%
2	journaldatabase.info Internet Source	1%
3	Submitted to Queen's University of Belfast Student Paper	1%
4	Submitted to Nottingham Trent University Student Paper	1%
5	mamcjms.in Internet Source	1%
6	Jining Yang, Daoyuan Si, Yanan Zhao, Chengyan He, Ping Yang. "S-amlodipine improves endothelial dysfunction via the	1%

RANK/RANKL/OPG system by regulating microRNA-155 in hypertension", Biomedicine & Pharmacotherapy, 2019
Publication

7	Submitted to University of Luton Student Paper	1 %
8	www.labome.org Internet Source	1 %
9	onlinelibrary.wiley.com Internet Source	1 %
10	pdfs.semanticscholar.org Internet Source	1 %
11	Submitted to Intercollege Student Paper	1 %
12	www.tandfonline.com Internet Source	1 %
13	Chunfeng Cai, Zongkui Zhou. "Structural empowerment, job satisfaction, and turnover intention of Chinese clinical nurses", Nursing & Health Sciences, 2009 Publication	<1 %
14	journals.sagepub.com Internet Source	<1 %
15	pesquisa.bvsalud.org Internet Source	<1 %

16	Fatemeh Hamidi, Forouzan Elyasi, Seyed-Nouraddin Mousavinasab, Arash Ghasemi, Zohre Keshavarz, Zohreh Shahhosseini. "Effect of a social network-based supportive program (WhatsApp) on the sexual self-concept of women with breast cancer: A single-blind-randomized controlled trial", Palliative and Supportive Care, 2022 Publication	<1 %
17	Yoichiro Hirata, Takeshi Soeki, Hirotsugu Yamada, Asuka Shiota et al. "A synthetic prostacyclin agonist, ONO-1301, ameliorates ventricular remodeling after acute myocardial infarction via upregulation of HGF in rat", Biomedicine & Aging Pathology, 2011 Publication	<1 %
18	karotenoido.info Internet Source	<1 %
19	Chuang, I-Chen, Chih-Min Yang, Tuzz-Ying Song, Nae-Cherng Yang, and Miao-Lin Hu. "The anti-angiogenic action of 2-deoxyglucose involves attenuation of VEGFR2 signaling and MMP-2 expression in HUVECs", Life Sciences, 2015. Publication	<1 %
20	Hiroyuki Nomura. "Comparison of photoselective vaporization and standard transurethral resection of the prostate on	<1 %

urodynamics in patients with benign prostatic hyperplasia", International Journal of Urology, 08/2009
Publication

21	Robert J. Carrasquillo, Sean W. Nealy, David S. Wang. "5-Alpha-reductase inhibitors in diseases of the prostate", Current Opinion in Endocrinology, Diabetes & Obesity, 2014 Publication	<1 %
22	Submitted to University of Auckland Student Paper	<1 %
23	Yi Tang, Ruo-li Wang, Dan-dan Ruan, Xin Chen et al. "Retrospective observation of the efficacy and safety of prostatic artery embolization combined with transurethral resection of the prostate and simple transurethral resection of the prostate in the treatment of large (> 100 mL) benign prostatic hyperplasia", Abdominal Radiology, 2021 Publication	<1 %
24	media.neliti.com Internet Source	<1 %

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

The Effect of Dutaseride and Tomato Extract Combination on Reducing Blood Loss after Transurethral Resection of the Prostate

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4