The efficacy of dutasteride and green tea combination towards angiogenesis and bleeding on BPH after TURP:
Study the effect on VEGF, MVD, and Hb

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Abstract - Trans urethral resection of prostate (TURP) is a standard procedure in benign prostate hyperplasia (BPH) management, however it may face with complication such as hemorrhage that may increase morbidity and mortality rate. This study is designed to find the efficacy combination dutasteride and green tea extract in reducing hemorrhage on TURP patients and to evaluate the anti-angiogenesis effect. Double Blind Randomized Controlled Trial Post Test Only Design with 80 subjects, randomized into 4 groups: three treatment groups (T1 with 0.5mg of dutasteride, T2 with 725mg of green tea extract and T3 with combination of 0.5mg dutasteride and 725mg of green tea extract and one control group (C) at least 14 days before TURP procedure. We compared the ΔHb (haemoglobin) to evaluate the hemorrhage status and define the VEGF expression and MVD count to evaluate the angiogenesis changes between four groups. The study revealed ΔHb (pg/mL) for T1(-0.20±0.067) T2(-0.18±0.081) T3(-0.14±0.092) and C(-0.40±0.246). VEGF expression were T1(12.90±15.509), T2(11.60±9.121), T3(3.60±1.667) and C(20.20±17.386). MVD count median were T1(33), T2(31.5), T3(24) and C(42). The result from between subject effect tests showed statistically significantly reduce ΔHb, VEGF expression and MVD count. Multivariate analysis showed that the combination of dutasteride and green tea significantly reduce the hemorrhage during TURP (ΔHb) by decreasing the MVD. Administration of oral combination of 0.5mg dutasteride and 725mg of green tea extract, for at least 14 days prior to undergoing TURP significantly reduce the hemorrhage during TURP by decreasing the MVD.

Keywords: VEGF; MVD; Hb; Dutasteride; Green Tea

I. INTRODUCTION

Benign prostate hyperplasia (BPH) is a disease in elderly. BPH is the second most frequent disease found in urological clinics in Indonesia, just behind urinary tract stone (Fadlol and Mochtar, 2005). Trans urethral resection of prostate (TURP) is a gold standard treatment to reduce the lower urinary tract symptoms and urinary retention in BPH patient that untreatable with medication. The most common complication, both during and post operation is hemorrhage that significantly affect the morbidity and mortality (Shanmugasundaram et al., 2007; Kim et al., 2015; Boccon et al., 2005; Hahn et al., 2007).

The pathologic process on BPH involves the angiogenesis, increasing number and surface area of prostate vessels, that resulted in hemorrhage during TURP procedure. A number of studies has tried to find the factor to reduce angiogenesis (anti angiogenic therapy), one of them used 5-alpha reductase inhibitor, inhibits the conversion of testosterone into dehydrotestosterone (DHT) that trigger the prostate enlargement (Chapple, 2004). 5-alpha reductase inhibitor also plays important role in androgen dependent angiogenic growth factor reduction, such as VEGF, sub urothelial microvessel density and blood vessels reduction, resulting prostate size reduction and apoptosis induction (Chapple, 2004; Clark et al., 2004). This type of drug consists of finasteride and dutasteride. Dutasteride selectively inhibits both 5-alpha reductase isoenzym (type 1 and 2). Both of finasteride and dutasteride are beneficial in reducing hemorrhage during TURP procedure. They have a distinct pharmacokinetic system, dutasteride has a longer half life and some studies has mentioned that dutasteride is more...
**Table 1. Demographic and clinical characteristic of subjects included in current study**

<table>
<thead>
<tr>
<th>Confounding Factors</th>
<th>C</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>70.3 ± 6.626</td>
<td>69.9 ± 8.950</td>
<td>68.1 ± 7.732</td>
<td>69.5 ± 9.944</td>
<td>0.855</td>
</tr>
<tr>
<td>Prostatic weight (gram)</td>
<td>39.4 ± 12.923</td>
<td>45.3 ± 17.946</td>
<td>46.0 ± 17.096</td>
<td>43.7 ± 14.737</td>
<td>0.555</td>
</tr>
<tr>
<td>The duration of the treatment (day)</td>
<td>16.20 ± 1.704</td>
<td>15.95 ± 1.572</td>
<td>16.00 ± 1.414</td>
<td>15.85 ± 1.461</td>
<td>0.908</td>
</tr>
<tr>
<td>The duration of catheter placement (day)</td>
<td>17.53 ± 2.129</td>
<td>18.00 ± 2.152</td>
<td>17.60 ± 2.349</td>
<td>17.00 ± 1.622</td>
<td>0.532</td>
</tr>
<tr>
<td>The duration of the TURP (minute)</td>
<td>34.40 ± 3.979</td>
<td>34.65 ± 3.514</td>
<td>35.45 ± 2.762</td>
<td>34.90 ± 3.007</td>
<td>0.782</td>
</tr>
<tr>
<td>The irrigant fluid needed during the TURP (litre)</td>
<td>6.95 ± 0.780</td>
<td>7.04 ± 0.719</td>
<td>7.11 ± 0.596</td>
<td>6.97 ± 0.603</td>
<td>0.868</td>
</tr>
<tr>
<td>The time needed after the TURP procedure to obtain the blood subjects for Hb examination (minute)</td>
<td>85.00 ± 13.514</td>
<td>84.00 ± 15.526</td>
<td>84.50 ± 14.681</td>
<td>83.50 ± 9.473</td>
<td>0.807</td>
</tr>
</tbody>
</table>

T1 = group of 0.5 mg dutasteride / day, T2 = group of 725 mg green tea extract / day, T3 = group of the combination of 0.5 mg dutasteride and 725 mg green tea extract / day. C = the control group (placebo).
III. RESULTS AND DISCUSSION

We recruited 90 subjects with urinary retention, planned to undergo TURP procedure, and all of them fulfilled the inclusion and exclusion criteria. The subject receive the treatment at least 14 days before TURP procedure.

Seven subjects were out of the analysis: 2 of them were unable to comply the treatment (both from T1), 3 subjects were aborted due to comorbid of New York Heart Association (NYHA) level III congestive heart failure (CHF) (2 from T2 and 1 from T3), 3 subjects were lost during follow-up period (2 from C group). We managed to have a data set from 83 subjects to be analyzed.

The average age of the subjects is 69.44 ± 8.287 years old with 48 and 87 as the youngest and the oldest respectively. The average prostatic weight is 43.62 ± 15.7 grams, with 18.6 and 85 grams as the minimum and maximum weight. The duration of the treatment are 16 ± 1.5 14 and 19 days for the average the shortest and longest duration respectively. The duration of catheter placement are 17.53 ± 2.129 14 and 23 days for the average the shortest and longest duration respectively. The duration of the TURP are 34.85 ± 3.307 27 and 44 minutes in average the shortest and the longest duration respectively. The irrigant fluid needed during the TURP were 7.016 ± 0.669 litres, 5.8 litres and 8.8 litres in average minimum and maximum volume respectively. The time needed after the TURP procedure to obtain the blood subjects for Hb examination were 85 ± 13.36, 50 and 120 minutes for the average minimum and maximum values respectively. The Mann-Whitney test showed a significant difference of ΔHb between T2 and T3 groups and also T1 and T3 groups. There is no significant difference in ΔHb between T1 and T2. Therefore, ΔHb in T3 is significantly lower compared with T1 and T2.
The VEGF expression in treatment groups (T1, T2, T3) was significantly different compared to control group. There is significant difference in VEGF expression reduction between T2 and T3 groups and T1 and T3 groups. There was no significant difference between T1 and T2. Therefore, the VEGF expression in T3 were significantly lower compared to T1 and T2.

The post hoc test analysis showed significant reductions in group T1, T2, T3 compared with K. There were significant MVD count between T2 and T3, and also between T1 and T3, but not in T1 and T2. Therefore MVD count in T3 was much more significant compared with T1 and T2.

Multivariate analysis showed that the combination of dutasteride and green tea significantly reduce the number of bleeding (ΔHb) by decreasing the MVD. The possible factors that affect the hemorrhage volume during TURP procedure in all study subjects are: age, prostate volume, medical treatment duration, Catheter placement duration, operation time, irrigant fluid volume, and time until blood sample drawn after TURP procedure. All off them are well controlled and unable to affect the validity of study results (Walsh and Retik, 1998).

The study showed that the lowest amount of bleeding complication (ΔHb) is in the T group. The study also showed that combination of dutasteride and green tea reduced the hemorrhage count due to MVD count suppression.

Angiogenesis is an adaptation process by creating a new blood vessel to respond the environmental changes that endanger the tissue. Angiogenesis itself can be pathological or physiological. The physiologic type occurs during growth of the tissue healing and menstrual cycle in women. The pathological type occurs during malignancy or infectious disease, vascular formation, and other hypoxic-induced condition (Carmeliet and Jane, 2000). The angiogenesis starts with trigerring factors, and it most case it will be hypoxic status. In tumor, the distant between the vessel and the cell affects the oxygen level diffusing into the cells. This condition, known as hypoxia, it will trigger the hypoxic-indicible factor 1α (HIF-1α) and increase the transcription process of angiogenic factor genes. HIF-1α also plays role on wether the cell move into apoptotic mode or not. The mechanical stress (intratumoral high pressure), inflammation/immune response, and genetic mutation on oncogene or tumor supressor gene, also play their part in angiogenesis (Hicklin and Ellis, 2005).

Hypervascularisation in prostate usually accounts for hemorrhage in BPH patient. The angiogenesis supression can be tried by manipulating the hormone that inhibits the testosterone. The blood flow into the prostate will be very affected by the testosterone (Lee, 1996). Testosterone triggers the growth and maintain prostate epithelium. In this study, green tea has a role in supressing the hemorrhage, reducing need of tranfusion, reducing VEGF expression and MVD count into the level that more significant with the combination of dutasteride and green tea.

Combination of both dutasteride and green tea extract, given as anti angiogenic therapy in TURP procedure for BPH patient. Green tea inhibits the P38k/Akt pathway, reduce the VEGF production, and finally reduce the angiogenesis (Steel et al., 2000; Yang et al., 1998; Lill et al., 2003). Active component in green tea, EGCG; inhibits cell growth and endothelial cell growth. EGCG is a strong antioxidant and effectively inhibits the carcinogenic activity. EGCG inducing the phase-II detoxification enzymes, such as peroxidase, stop the cycle cell, induce apoptosis and prostate growth (Robb and Brown, 2001). EGCG also inhibits another growth factors in prostate, for example basic fibroblast growth factor (bFGF); epidermal growth factor (EGF), insulin-like growth factor (IGF). Dutasteride reduces the growth factors by inhibiting the conversion testosterone into DHT, therefore reducing the androgen activity (Mc Conenel et al., 1992; Ku et al., 2009). Both mechanism reduce the prostatic VEGF and MVD, minimize hemmorhage during TURP, reduce the haemoglobin
decrease during operation, and reducing transfusion rate after TURP procedure.

IV. CONCLUSIONS

It can be concluded that administration of oral combination of 0.5 mg dutasteride and 725 mg extract green tea once daily, for at least 14 days prior to undergoing TURP, significantly reduce the hemorrhage during TURP procedure, by decreasing MVD.

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REFERENCES


