The Role of Vitamin E in Peyronie's Disease

Ricky Suritno
St. Vincentius General Hospital, Singkawang, West Borneo, Indonesia

ABSTRACT

Peyronie's disease (PD) is a disorder of tunica albuginea of corpus cavernosum characterized by the formation of plaque and fibrosis. Oral therapy is a promising non-operative modality. Vitamin E as a well-known antioxidant, is the oldest substance used since 1948 to treat Peyronie's disease. The mechanism is to inhibit the production of inflammatory reactive oxygen species (ROS). There is still controversy over the effectiveness of vitamin E in Peyronie's disease management.

Keywords: Peyronie's Disease, Vitamin E, Antioxidant, Treatment

ABSTRAK

Penyakit Peyronie merupakan gangguan jaringan ikat tunica albuginea dari corpus cavernosum yang mempunyai karakteristik pembentukan plak dan fibrosis. Terapi oral merupakan modalitas terapi non operatif yang menjanjikan. Vitamin E sebagai antioksidan yang sudah banyak dikenal, merupakan terapi tertua sejak tahun 1948. Mekanismenya adalah untuk menghambat produksi *reactive oxygen species* (ROS). Sampai saat ini efektivitas vitamin E dalam penanganan penyakit Peyronie masih kontroversial. **Ricky Suritno. Peran Vitamin E dalam Tatalaksana Penyakit Peyronie**

Kata kunci : penyakit peyronie, vitamin E, antioksidan, terapi

INTRODUCTION

Peyronie's disease (PD) is a connective tissue disorder of tunica albuginea of corpus cavernosum characterized by the formation of plaque and fibrosis.[1] The etiology is still unknown. However, repetitive microvascular injury and penile trauma are hypothesized to cause the development of PD.[2,3] The development of PD is classified into two stages. Acute inflammatory stage usually lasts for 12 to 18 months. In this stage, penile curvature started to form, and usually presents as penile pain, not only during erection, but also during flaccid phase. In fibrotic stage, the progression of penile curvature has already stabilized, although the symptoms of chronic pain still present. Several risk factors have been proved to influence the development of the disease, including diabetes mellitus, hypertension, dyslipidemia, ischemic cardiomyopathy, smoking, and excessive alcohol consumption.

It is estimated that about 3.2-13% of adult male population is affected. Several studies also found a connection of Peyronie's disease with Dupuytren's contracture, and it is estimated that 15.4%-22.1% of Dupuytren's contracture cases is coexisted with PD. Around 15-30% cases of Dupuytren's contracture are also affected by PD.[4]

Management of Peyronie's disease is classified into two approaches, non-operative and surgical. Non-operative treatment is divided into three groups**: oral** treatment that consist of vitamin E, potassium para-amino benzoate, tamoxifen, colchicine, acetyl ester of carnitine, pentoxifylline, PDE5I; **intralesional** treatment (injection into the plaque) with steroids, verapamil, clostridium collagenase, and interferon; **topical** treatment with verapamil, iontophoresis, extracorporeal shock wave, and traction and vacuum devices.[2,5]

There is still controversy over the efficacy of oral treatment in Peyronie's disease. Some studies showed no significant benefit, particularly with vitamin E. There is also a conflicting evidence of the adverse effect of high dose vitamin E to cardiovascular effect in long term use. In contrast, a recent study showed a promising result in the early stage and may be beneficial in clinical practice if proven to be effective.

Vitamin E is the oldest substance used since 1948 to treat Peyronie's disease. Scardino and Scoot first found that vitamin E could reduce plaque size and improve curvature in Peyronie's disease.[6] Contrarily, in 1983, a randomized controlled trial (RCT) by Pryor and Farrel found no significant effect of vitamin E to reduce symptoms[7]. Later, Safarinejed et al., (2007) also did not find a significant effect of vitamin E in the treatment of Peyronie's disease.[8] Interestingly, recently several studies showed a significant effect of vitamin E when combined with other modalities.[9,10]

MECHANISM OF PEYRONIE'S DISEASE

Until recently, the etiology of Peyronie's disease has been hypothesized by penile trauma and repetitive microvascular trauma (**Figure 1**).[2] Several explanations have been proposed to describe the mechanism; deposition and accumulation of fibrin after several penile traumas is one of the main popular hypothesis. Production of fibrin attracts inflammatory cells such as neutrophil and macrophages that release ROS, which later activate NF-kB and induce NOS. NOS induce the production of nitrite oxide radical,

Alamat Korespondensi *email: ricky.suritno@gmail.com*

that damage penile tissue and later form plaque.[11]

Knowledge on ROS and oxidative stress plays a significant role in treating this disease. However, approach to counteract the impact of free radical in the development of penile plaque in Peyronie's disease with antioxidant such as vitamin E is still controversial, and more studies required to generate the conclusive effect of this treatment. ROS is free radical derived from oxygen with highly reactive oxidizing agent. ROS consist of superoxide (O_2^-) anion, hydrogen peroxide (H2O2) and very reactive hydroxyl (OH) and peroxyl (ROO) radical and some nitrogen derived free radical like nitric oxide (NO) and peroxynitrite anion (ONOO-). [12]

Histopathology of Peyronie's disease consists of inflammation process that can be seen from chronic lymphocytic and infiltration of plasmacytic in tunica albuginea.

Biosynthesis of collagen is caused by the variety of endogenous and exogenous factors such as interleukin-1, tumor necrosis factor, epidermal growth factor, and transforming growth factor beta (TGF-β). TGF-β is an important cytokine for tissue repair, which in the presence of trauma, the increment of TGF-β may lead to fibrosis and plaque formation. Further, under hypoxia and oxidative stress, activation of nuclear kappa B (NF-κB) regulates the adhesion of molecules.

ROLE OF VITAMIN E

Vitamin E requires bile acid for absorption and about 25% can easily be absorbed orally from foods. Absorbed vitamin E will be stored in adipose tissue, liver, and muscle.

Vitamin E (α-tocopherol) is a fat-soluble vitamin with antioxidant effect. Vitamin E works as a scavenger against hydroxyl and lipid peroxyl radical and inhibits ROS (**Figure 2**). Other than antioxidant, vitamin E also immunomodulation and antiplatelet effect.[12,13] As an antioxidant, vitamin E interacts with ROS to restore the molecule into its normal state.[14] Additionally, vitamin E also prevent membrane lipid peroxidation, elevate cellular GSH levels, reduce protein glycosylation, blood triglyceride and thromboxane levels.[11]

In terms of its antioxidant function, optimal

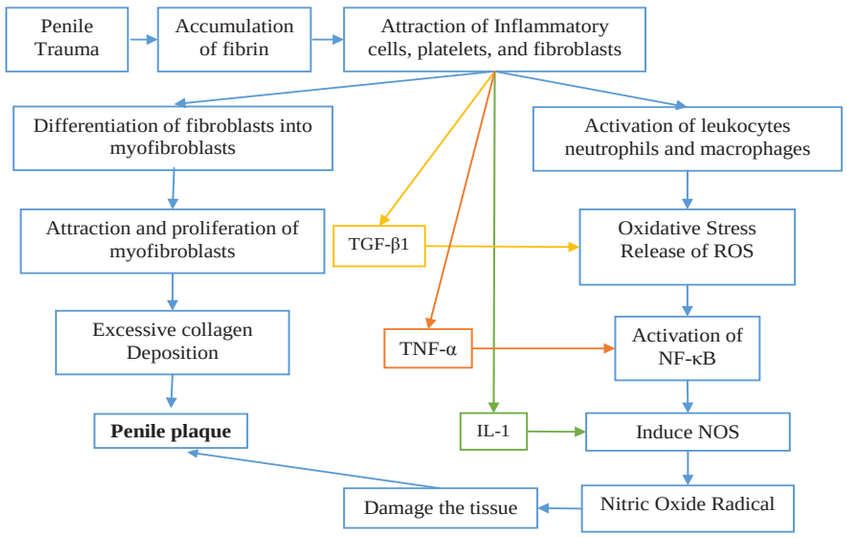

Fig 1. Pathophysiology of Peyronie's Disease[2]

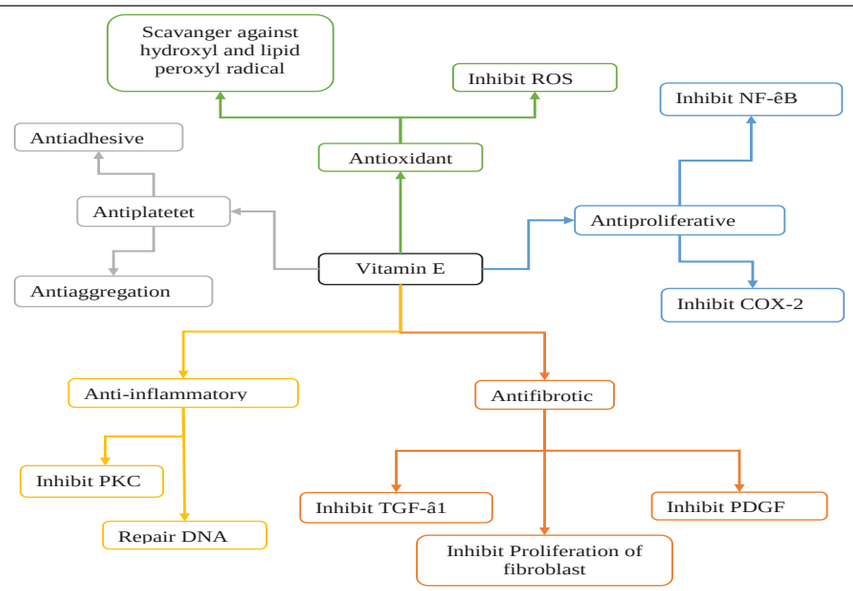

Fig 2. Function of Vitamin E

Table 1. Study Result (1)

	Study Group (vitamin E + propolis + blueberry + verapamil + topical diclofenac)	Control group (propolis + blueberry + verapamil + topical diclofenac)	P value
Plaque size reduction	-50.2%	-35.8%	0.027
Improvement of curvature	96.6%	48.8%	0.0001
Mean curvature	-12.25°	-6.73°	0.01

Table 2. Study Result (2)

Parameter	Group A	Group B	Group C	Group D	Group E	P value
Penile pain	-2.181	-3.416	-4.363	-4.692	-4.846	p = 0.002
Reduction in plaque volume	-23.431	-25.763	-28.435	-32.865	-50.942	p = 0.000
Decrease in penile curvature angle	-3.30°	-4.73°	-6.0°	-8.52°	-13.09°	p = 0.000
Improvement in IIEF-EF with ED ± SD	+ 0.8 ± 0.8	+ 2.1 ± 2.6	+ 2.4 ± 2.5	+ 3.2 ± 2.5	+ 4.4 ± 2.4	P = 0.047
Improvement in IIEF-EF score without ED ± SD	+ 0.4 ± 0.5	+ 0.6 ± 0.5	+ 0.8 ± 0.6	+ 1.2 ± 0.6	+ 1.4 ± 0.6	P = 0.000

vitamin E level also inhibits TGF-β production, D-alpha-tocopherol and α-tocopherol succinate as antifibrotic agent.[1] Vitamin E also inhibits NF-κB and has anti-cox2 mechanism as an anti-inflammatory agent. It can inhibit proinflammatory cytokine transcription and cell proliferation through a protein kinase C (PKC).[12] Vitamin E as antiplatelet work to inhibit platelet adhesion and aggregation.[11,12] Vitamin E can also repair DNA and improves endothelial function.[12]

THE EFFECTIVENESS OF VITAMIN E IN PEYRONIE'S DISEASE

Vitamin E is still used to treat Peyronie's disease because its low toxicity and not too expensive.[15] Some possible side effect in vitamin E medication are cerebrovascular event at large dose, nausea, vomiting, diarrhea, headache, and dizziness.[2,5]

Several studies had been done to see the effect of vitamin E in treating Peyronie's diseases.[6-10,16,17] AUA guidelines in 2015 stated that clinician should not offer therapy with vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, a combination of vitamin E with L-carnitine.[18]

Castro et al in 2003 reported that vitamin E combined with colchicine improved penile curvature and reduced plaque size in 45 participants randomized into two groups and observed for 6 months[16]. RCT study by Safarinejad in 2007[8] reported that vitamin E had similar curvature and plaque increase with the placebo group. The period of this study was 6 months. The efficacy of treatment was assessed by the international index of erectile function, visual analog scale for pain evaluation, intercourse satisfaction, penile curvature, plaque size and adverse drug effect. Inal et al [17]compared 3 group of treatment, vitamin E group, intralesional interferon alpha 2b, and combination of both modalities; They also didn't found significant effect

However, in 2012, Paulis et al showed better result with vitamin E in Peyronie's disease if combined with other medication, like decreasing curvature and plaque formation compared to medication that does not use the combination of vitamin E in their treatment. One of Pauli's controlled study with 70 participants investigate the benefit of vitamin E in Peyronie's disease, they randomly divided into 2 categories: [9]

- Study group are given vitamin E 600mg/oral/daily + propolis 600 mg/oral/daily + blueberry 160mg/oral/daily + verapamil 10 mg/every 2 weeks + iontophoresis with 5 mg daily (excluding the day of injection) + topical diclofenac 4% gel/twice a day
- Control group are given propolis 600 mg/oral/daily + blueberry 160mg/oral/daily + verapamil 10mg/every 2 weeks + iontophoresis with 5 mg daily (excluding the day of injection) + topical diclofenac 4% gel/twice a day

These two groups are observed for 6 months and the result from this study can be seen vitamin E has more effect in combination therapy in Peyronie's disease (**Table**).

Beside of plaque size reduction, improvement of curvature and improvement of mean curvature, the IIEF score was also better in the study group (p-value 0.025). Size of penile plaque only increase in control group 17.1% (p-value = 0.032). From this study, it can be seen the vitamin E still has effect in the treatment of Peyronie's disease or it can help in progression of Peyronie's disease

The other study had been done in 2017. Paulis et al reported the combination of antioxidant showed a good result in decreasing the symptom of the disease. In this study there were 120 participants randomized into 5 categories [10]

- Group A : Silymarin 200mg/orally/twice daily
- Group B :Silymarin 200mg/orally/twice daily + ginkgo biloba 250 mg/orally/once daily
- Group C :Silymarin 200mg/orally/twice daily + ginkgo biloba 250 mg/orally/once daily + Vitamin E 400 IU/orally/twice daily
- Group D :Silymarin 200mg/orally/twice daily + ginkgo biloba 250 mg/orally/once daily + Vitamin E 400 IU/orally/twice daily + Propolis 600 mg/orally/once daily + bilberry 160 mg/orally/once daily + topical diclofenac sodium 4% spray gel/once application per day
- Group E :Silymarin 200mg/orally/twice daily + ginkgo biloba 250 mg/orally/once daily + Vitamin E 400 IU/orally/twice daily + Propolis 600 mg/orally/once daily + bilberry 160 mg/orally/once daily + topical diclofenac sodium 4% spray gel/once application per day + PTX 100 mg twice a month

Results after 6 months : **(see table 2)**

In this study, vitamin E showed a better effect as a combination therapy. Even though the other group with more antioxidant, topical treatment, and PTX injection showed better effect. Vitamin E may not be enough for monotherapy in Peyronie's disease but showed better outcome if combined with other modalities.

CONCLUSION

Peyronie's disease is correlated with oxidative stress resulting in penile plaque**.** Peyronie's disease can affect the quality of life for the patient, such as penile pain, deformation and disturbing sexual life. Vitamin E has the mechanism to inhibit inflammatory ROS cell release, that may help to slow the progression of Peyronie's disease**.** Even though there are still some controversies, recent study show a good effect of vitamin E in combination therapy**.** No significant adverse effect of vitamin E was observed.

REFERENCES

1. Hussein A, Alwaal A, Luea T. All about Peyronie's disease. Asian J Urol 2015;2(2):70-8.
2. Hatzimouratidis K, Giuliano F, Muneer A, Salonia A, Verze P, Moncada I. Erectile dysfunction, premature ejaculation, penile curvature and priapism. EAU Guidelines 2016. pp.32-43.
3. Somers KD, Dawson DM. Fibrin deposition in Peyronie's disease plaque. J Urol 1997;157:311-5.
4. Vanni AJ, Bennett NE. Current treatment and management of the acute phase of Peyronies's disease. Arch ESP Urol 2009;62, 614–22.
5. Hellstrom W. Medical Management of Peyronie's disease. J Androl 2009;30(4): 397-405.
6. Scardino PL, Scott WW.The use of tocopherols in the treatment of Peyronie's disease. Ann NY Acad Sci 1949;52(3):390–6.

7. Pryor JP, Farrell CF. Controlled clinical trial of vitamin E in Peyronie's disease. Prog Reprod Biol 1983;9:1–45.
8. Safarinejad M. POS-01.89: Comparison of vitamin E and propionyl-l-carnitine, separately or in combination in patients with early chronic Peyronie's disease: a double blind, placebo-controlled, randomized study. Urology 2007;70(3):217
9. Paulis G, Brancato T, D'Ascenzo R, De Giorgio G, Nupieri P, Orsolini G, Alvaro R. Efficacy of vitamin E in the conservative treatment of Peyronie's disease: legend or reality? A controlled study of 70 cases. Andrology 2012;1(1):120-8.
10. Paulis G, Paulis A, Romano G, Barletta D, Fabiani A. Rationale of combination therapy with antioxidants in medical management of Peyronie disease: results of clinical application. Res Reports in Urology 2017; 9:129-39.
11. Sikk, S, Hellstrom W. Role of oxidative stress and antioxidants in Peyronie's disease. Internat J Impotence Res 2002;14(5):353-60.
12. Paulis G, Romano G, Paulis L, Barletta D. Recent pathophysiological aspects of Peyronie's disease: Role of free radicals, rationale, and therapeutic implications for antioxidant treatment—literature review. Advances in Urology 2017:1-17.
13. Joice G, Burnett A. Nonsurgical interventions for Peyronie's disease: Update as of 2016. The World J Men's Health 2016;34(2): 65.
14. Campbell J, Alzubaidi R. Understanding the cellular basis and pathophysiology of Peyronie's disease to optimize treatment for erectile dysfunction. Translat Androl Urol 2017;6(1:46-59.
15. Barrett-Harlow B, Wang R. Oral therapy for Peyronie's disease, does it work?. Translat Androl Urol 2016;5(3):296-302.
16. Prieto Castro R, Leva Vallejo M, Regueiro Lopez J, Anglada Curado F, Alvarez Kindelan J, Requena Tapia M. Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. BJU Internat 2003;91(6):522-4.
17. Inal T, Tokatli Z, Akand M, Özdiler E, Yaman Ö. Effect of intralesional interferon-alpha 2b combined with oral vitamin E for treatment of early stage Peyronie's disease: A randomized and prospective study. Urology 2006;67(5):1038-42.
18. Nehra A. et al. Peyronie's Disease: AUA. American Urological Association (AUA) Guideline 2015. pp.10-11.