Opinion:
Topical Valproate Solution for Hair Growth

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Citation

Abstract:
Valproate is used regularly in the treatment of various seizure disorders, bipolar disorder, migraine prophylaxis and off label in many other conditions. Alopecia or hair loss is cosmetic side effect of oral valproate administration. Hair loss with valproate is diffused, non-scarring and dose related. A large number of drugs may interfere with the hair cycle and produce hair loss. We have only few drugs like Minoxidil, Finasteride used for hair regeneration and both have its own side effects and limitations. In contrast to oral ingestions of valproate causing hair loss, early experiments with topical Valproic acid cream showed hair regeneration. Valproic acid cream is currently unavailable in the market, alternatively we do have valproate and divalproex solutions available in various strengths which have a potential to be used topically for hair regeneration. The side effects and cost of topical valproate solution could be much less than the available options in the market. Valproate solution topically has the potential to be used for hair growth.

Key Words: Valproate, hair, regeneration, topical solution

Introduction:
Valproate is used regularly in the treatment of various seizure disorders, bipolar disorder, migraine prophylaxis and off label in many other conditions [1, 2]. It is a histone deacetylase inhibitor, exerting its action through modification of chromatim structure and gene expression. It is also involved in the modulation of ERK and Wnt-beta-Catenin signalling pathways [3, 4]. Valproate inhibits the cellular sodium influx by blocking voltage-dependent sodium channels and induces chloride influx by gamma hydroxyl butyric acid (GABA)-mimetic effect. It also reduces the release of GABA, thereby attenuating neuronal excitation induced by glutamate receptors [5]. Valproic acid (VPA) also interferes with arachidonate and inositol metabolisms in vivo. Alterations in multiple gene expressions are reported with valproate treatment. These genes are known for their role in cell survival, transcriptional regulation, ion homeostasis and signal transduction. Valproic acid also binds to activator protein-1 DNA and directly inhibits histone deacetylases [6].

Oral valproate and hair loss
The common adverse drug reactions reported in valproate administration are tremor, weight gain, gastrointestinal disturbances, liver dysfunction, metabolic acidosis, thrombocytopenia and hair loss. Alopecia or hair loss is cosmetic side effect of VPA administration [7]. Hair loss with valproate is diffused, non-scarring and dose related. Recognition of cosmetically significant side effects on hair is necessary and neglect of which might result in poor compliance [8]. Starting with a low dose and progressive increase in the dosage is considered as a key strategy in counteracting valproate induced hair loss [9]. There are studies, case series and reports on VPA induced hair loss [8, 10, 11, 12, 13]. The incidence of oral valproate causing hair loss are 3.5% [14], 6% [15] and 12% [12] among various studies.

Topical valproate and hair growth
A large number of drugs may interfere with the hair cycle and produce hair loss. We have only few drugs like Minoxidil, Finasteride used for hair regeneration and both have its own side effects and limitations [16]. In contrast to oral ingestions of valproate causing hair loss, experiments with topical valproic acid showed hair regeneration. An experimental study in South Korea was done by taking murine models and human dermal papilla cells to check the effect of topical valproic acid in androgenic alopecia. Valproic acid was applied topically to male C3H mice and hair re-growth was noted. Effects of valproic acid and minoxidil on human dermal papilla cells were compared. It was seen that beta-catenin, Alkaline phosphatase, and BMP4 expression was greatly increased by treatment with valproic acid, but not minoxidil [17]. A randomized, double-blind, placebo-controlled clinical trial was done to assess the efficacy of topical valproate for treating...
androgenic alopecia. Male patients with moderate androgenic alopecia underwent treatment with either VPA (sodium valproate) 8.3% or placebo spray for 24 weeks. The primary endpoint for efficacy was the change in hair count during treatment, which was assessed by photo-trichogram analysis. The mean change in total hair count was significantly higher in the VPA group than in the placebo group [18]. Valproic acid is known to inhibit glycogen synthase kinase 3β and activation of Wnt/b-catenin pathway, which in turn, is associated with hair regeneration and anagen induction. In preclinical studies with valproic acid conducted on rats, it was shown that administration of higher dosages of VPA resulted in increased acetylation and activation of histone-3 and PI3K pathway proteins. It is also reported to have cytoprotective abilities when administered in split lower doses [19].

In a randomized interventional study, 7.2% spray of sodium valproate applied twice daily on scalp up to 24 weeks showed the efficacy of VPA spray on androgenic alopecia. Study subjects included patients in the age group of 19-45 years, diagnosed with androgenic alopecia according to Hamilton and Norwood grade III-IV and those whose follow-up would be possible up to 24 weeks. Subjects with severe medical conditions and received alopecia treatment with surgical methods such as hair transplantation were excluded from the study. Primary outcome parameters assessed were linear hair growth rate and secondary outcome measures included final hair density over a time frame of 24 weeks. All the measures were compared with a placebo treated group [20].

**Conclusion**

Valproic acid cream is currently unavailable in the market, alternatively we do have Valproate and Divalproex solutions available in various strengths which have a potential to be used topically for hair regeneration. The side effects and cost of topical valproate solution could be much less than the available options. Our hypothesis is valproate solution topically can be used for hair growth.

**Acknowledgements:**

This opinion article was written while working on an Indian Association of Private Psychiatry (IAPP) grant project on Valproate and hair loss.

**References**