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Comparison between topical tacrolimus and potent topical steroids in treatment of childhood vitiligo

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[**Abstract**] **Objective** To assess which of topical tacrolimus and topical highly potent steroids, is more effective and safer in the treatment of pediatric vitiligo. **Methods** The PubMed, Cochrane library, Scopus and CINAHL plus databases were retrieved. The search was confined to English language articles. The randomized controlled trial(RCT) articles were included in our study. The quality of the identified articles was examined by using the CASP Randomised Controlled Trials Checklist. **Results** As a result, there were only a few studies related to the comparison. However, there were only two RCTs regarding a comparison of topical tacrolimus 0.1% and clobetasol propionate 0.05% in childhood vitiligo. **Conclusion** When the body surface area (BSA) involved in the child is <20%, and the disease is not rapidly spreading, topical therapy is the first choice. Topical tacrolimus may be considered as an alternative therapy for childhood vitiligo, especially for acrofacial and segmental types, before considering other modalities, but still need to observe long-term side effects.

[**Key words**] topical tacrolimus; potent topical steroids; children; vitiligo
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Vitiligo is a relatively common, acquired and depigmented skin disease[1]. Around half or the patients have onset prior to the age of 20 years[2]. Childhood vitiligo most often presents first on the head or neck and it seems to be a distinct subtype of vitiligo[3]. At the moment there is no cure for vitiligo, but many treatments can often slow down its progress or, in some cases, bring about repigmentation[4]. Therefore, timely treatments and choosing medications with fewer side-effects are very important for children. This is intended to minimize psychosocial and long lasting effects on the self-esteem of the affected children and their parents[5]. However, topical steroids have been observed to have many side effects which can affect children's appearance[6]. Since 2002, some studies have confirmed the calcineurin inhibitor tacrolimus is effective in the treatment of vitiligo and is catching up fast[7]. Additionally, there have been a few studies to observe the safety of tacrolimus[8-10]. Unfortunately, there is a lack of literature reviews to compare the efficacy and safety of these topical treatment modalities in childhood vitiligo. Furthermore, most authors have to extrapolate the results form adults' data[11]. Therefore, it is essential to survey the findings and results from different studies and research in order to make the decision regarding the choice of suitable treatments for childhood vitiligo.

1 Materials and Methods

Searches were made of the PubMed, Cochrane library, Scopus and CINAHL plus databases. The search was confined to English language articles. After reading these papers, a retrospective review was performed of two randomised controlled trials (RCTs) regarding a comparison of topical tacrolimus 0.1% and clobetasol propionate 0.05% in childhood vitiligo. The quality of the identified articles was examined by using the CASP Randomised Controlled Trials Checklist (table 1).

Table 1 CASP Randomised Controlled Trials Checklist

Bias	Ho et al.[12]	Lepe et al.[13]
The trial addresses a clearly focused issue	Low risk	Low risk
Random sequence generation (selection bias)	Low risk["Randomized into three arms: CP 0.05% ointment(n=30), T 0.1% ointment(n=31), Placebo (n=29)"]	Low risk ("The method of randomization used was the technique of permuted block randomization for right or left selection.")
Allocation concealment (selection bias)	Not clear from the text	Not clear from the text
Were all of the patients properly accounted for at its conclusion?	High risk (10 dropout, dropout rate 10/100=10%)	Low risk (No dropout)

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Continued Table 1 CASP Randomised Controlled Trials Checklist

Bias	Ho et al.[12]	Lepe et al.[13]
Blinding (performance bias and detection bias) participants/clinicians	Low risk ("An identification number was assigned to each patient after registration to a randomization study group by the pharmacy personnel. These numbers were used throughout the study during data collection, later compiled by an independent research assistant, then analyzed by an independent statistician.")	Low risk ("The medications were in exactly the same containers packed by a person unaware of the study.")
Were the groups similar at the start of the trial? (age, sex, social class)	Low risk (Demographic data and clinical characteristicsof the vitiligo (segmental and non-segmental, extent, location) were obtained from each patient." n = 100, 2—16 yrs, 50 M/50 F)	Low risk (n=20, 5-17yrs, 4M/16F)
Outcomes were measured, clearly specified	High risk ("There were no validated outcome measures as thephotographs were not always standardized and the size was not reliably assessed.")	Low risk ("The repigmentation was evaluated by color slides at baseline and again at every 2-week visit. Characteristics of pigment, time of response, symptoms, telangiectasias, and atrophy were evaluated every 2 weeks.")
Confidence limits	High risk (" Results in the facial group, 58% of theCP 0.05% group responded successfully compared with58% of the T 0.1% group, and …compared with 23% of theT 0.1% group(P>0.05).")	High risk ("Clinical evaluation of the results showed no statistically significant differences between treatments(P>0.05, Kolmogorov-Smirnov test). However, computerized morphometric evaluation showed that tacrolimus was a significantly more effective treatment (P=0.005, paired t test).")
The results can be appliedin the local population)	Not clear from the text	Not mentioned in the study
Were all clinically important outcomes considered?	Low risk("Secondary outcomes on adverse events, patterns of repigmentation and spontaneous repigmentation were obtained.")	High risk (No consideration was given spontaneous repigmentation)
Are the benefits worth theharms and costs?	Costs not mentioned in the study.	Costs not mentioned in the study.
Funding	Low risk (This self-initiated study was supportedby a research grant from Astellas, Canada. This clinical study remained self directed. Astellas had no involvement in study design, data collection, data analysis, manuscript and publication decisions.	No precise information

Table 2 Details of two RCTs.

Author/s	Ho et al.[12]	Lepe et al.[13]
Study design	A double-blind, randomized, placebo-controlled trial	Randomized double-blind trial
No. subjects	100	20
Agerange(mean age)	2—16 yrs	5—17 yrs
Male/Female	50 M/50 F	4 M/16 F
Treatment	Randomized into three arms: CP 0.05% ointment(n=30), T 0.1% ointment(n=31), Placebo(n=29)	0.1% tacrolimus or 0.05%clobetasol propionate twice per day to 2lesions of similar size on the left and right
Duration/Follow-up	6 mos	2 mos
Repigmentation rate	In the facial group, responded successfully rate: CP 0.05% *vs.* T 0.1% was 58% *vs.* 58% (P=0.57). In the non-facial group, responded successfully rate: CP 0.05% *vs.* T 0.1% was 39% *vs.* 23% (P=0.30). There wasa significant difference in response between CP 0.05% *vs.* placebo (P<0.01) and T 0.1% *vs.* placebo(P=0.0004).	Eighteen (90%) of the 20 patients experienced somerepigmentation. The mean percentage of repigmentation was 49.3% for clobetasol *vs.* 41.3% for tacrolimus
Notes	No significant clinical adverse events were noted in any group.	3 patients using clobetasol presented atrophy telangiectasia; tacrolimus caused a burning sensation in 2 lesions.

2 Conclusion

The two RCTs demonstrated both topical tacrolimus and topical CS had similar efficacy in repigmenting paediatric vitiligo. The authors stated no significant clinical adverse events were noted in any group[12]. Another RCT showed lesions in 3 patients using clobetasol presenting atrophy and 2 lesions incurred telangiectasias; tacrolimus caused a burning sensation in 2 lesions[13]. When the body surface area (BSA) involved in the child is<20%, and the disease is not rapidly spreading, topical therapy is the first choice. Topical tacrolimus may be considered as an alternative therapy for childhood vitiligo, especially for acrofacial and segmental types, before considering other modalities, but still need to observe long-term side effects.

3 Discussion

Topical tacrolimus has similar efficacy as highly potent topical steroids (CP 0.05% ointment) in the treatment of childhood vitiligo. Although topical tacrolimus has some side effects, such as burning or pruritus, compared with topical CS, the studies showed fewer and lighter side effects had been observed. Tacrolimus does not interfere with collagen synthesis or have an effect on keratinocyte proliferation in vitro[14]. Due to segmental vitiligo more commonly occurs in children with characteristics of fewer lesions and less body skin involvement[15-18], there is some merit of tacrolimus in the treatment of childhood vitiligo, such as using on sensitive areas and no atrophy, telangiectasia, and ocular complications. It is also useful for use on the acrofacialis.

There is a need to consider that topical steroids use could cause steroid acne on the face, upper chest, neck and back and systemic absorption of topical steroids could occur especially in younger children and can lead to iatrogenic Cushing syndrome[19]. Hence, the current European Dermatology Forum consensus group guidelines recommend topical calcineurin inhibitors as a first line treatment for the face and neck because of lesser side effects[20]. Nevertheless, mid to high potent topical steroids are still the first line treatment for body vitiligo in children except genital and intertriginous areas[19]. There must some tips to improve efficiency and avoid side effects of topical steroids usage on childhood vitiligo. Firstly, the high potency topical steroids better not to be used for longer than 2－4 months[21]. Secondly, depends on the condition, usage of topical potent steroids as a sequential or discontinuous or (sequential and discontinuous) combination should be schemed. For instance, one week on one week off or weekend only usage helps to minimize its non-desired effects[19]. Thirdly, topical steroid sparing agents should be considered in long term use on the vitiliginous areas on the body. For example, pimecrolimus cream which has been shown effective to repigment vitiligo leasions in a comparable level with clobetasol in a split body studies[22]. Fourthly, addition of oral zinc supplementation with topical steroids leads to higher response rate than topical steroids alone[23]. Lastly, topical Vitamin D derivatives should be used together with topical steroids[24].

Tacrolimus was first reported in 2002 to be effective in the treatment of vitiligo[25]. Until now there have been only two RCTs compared with these two medications in the treatment of childhood vitiligo. There is still a lack of large sample size research and long duration observation of the safety of tacrolimus. In addition, Abu et al.[26] reported molluscum contagiosum infection was suspected during the treatment of vitiligo with tacrolimus ointment and Kanwar et al.[27] stated that, in 2005, the Pediatric Advisory Committee of US FDA implemented a black box warning for tacrolimus and pimecrolimus due to the lack of long-term safety data and the potential risk of the development of malignancies[26-28]. However, McCallum et al. showed extensive safety data of the 8-year availability when there was no increased incidence for cutaneous infections, and no evidence suggesting an increased risk of lymphoma or nonmelanoma skin cancer in adults and children[29]. So a conclusion about a firm long-term safety outcome cannot be drawn.

According to the results of the chosen papers, the repigmentation is associated with proper patient selection. The best response seen was in lesions over face and neck in many of the studies. Since the initial report of repigmentation in vitiliginous lesions by tacrolimus in adults, it has been observed that tacrolimus had similar efficacy as potent topical steroids, but fewer adverse effects[30]. However, both of the studies which I chose were using 0.1% tacrolimus ointment. Side effects such as pruritus and burning were still reported. It is worth researching whether a lower concentration of tacrolimus has similar efficacy with much fewer side effects. Moreover, there is a possibility of spontaneous repigmentation. It seems that large enough samples are quite essential. In addition, the results can be impacted by no standard measurement. Tacrolimus has proposed that there is different efficacy in different Fitzpatrick Skin Types and it is superior to Fitzpatrck Skin Typers 3 to 4[31]. Tacrolimus had been observed more response in the summer than in the winter[32]. Last but not least, Byun et al. treated one child with vitiligo successfully combination helium-neon laser and 0.03% topical tacrolimus. There should be more consideration for childhood vitiligo treatment in the future[33].

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