

## The effect of topical calcipotriol or zinc on tuberculin skin tests in hospitalised South African children

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### SUMMARY

**BACKGROUND:** The tuberculin skin test (TST) is used to help diagnose tuberculosis (TB) in acutely ill hospitalised children.

**OBJECTIVE:** To investigate the potential augmentative effect of topical calcipotriol (a vitamin D analogue) or zinc on TST induration.

**METHODS:** Three TSTs were performed among 64 hospitalised children; each site was covered with topical aqueous cream (control), calcipotriol or zinc and assessed 24 and 48 h later by investigators blinded to all topical applications.

**RESULTS:** TSTs were reactive in 15 (23.4%) children, of whom 13 (20.3%) were TST-positive. Topical calcipotriol and zinc induced TST positivity in two children with reactive but negative control TSTs. These treatments, however, did not significantly increase TST positivity

rates. In children with reactive TSTs, the median 48 h induration diameter was not significantly different between the control, calcipotriol- or zinc-treated groups, which were respectively 12.0 (25%-75% IQR 5.0 - 18.0), 14.0 (25%-75% IQR 10.0 - 15.0) and 12.0 (25%-75% IQR 8.0 - 15.0) mm. Topical treatments did not induce TST reactivity or TST positivity in children with culture-confirmed TB disease ( $n=4$ ), human immunodeficiency virus infection ( $n=18$ ) or kwashiorkor ( $n=9$ ).

**CONCLUSIONS:** Topical calcipotriol or zinc does not induce TST reactivity or significantly increase TST positivity rates in acutely ill hospitalised children. However, further studies are required to assess the effects of topical treatments on TST positivity in severely malnourished children.

**KEY WORDS:** vitamin D; Mantoux; HIV; malnutrition

THE TUBERCULIN SKIN TEST (TST), together with suggestive clinical and chest radiological signs, is commonly used to diagnose *Mycobacterium tuberculosis* disease in acutely ill hospitalised children admitted to health facilities in sub-Saharan Africa, a region burdened by the twin epidemics of the human immunodeficiency virus (HIV) and tuberculosis (TB).<sup>1</sup> The TST, however, is often non-reactive in malnourished and immune-suppressed children with *M. tuberculosis* infection.

The application of topical treatments may induce or increase TST induration, as is the case with candida skin test reactivity.<sup>2</sup> The application of topical zinc sulphate enhances TST reactivity in elderly subjects,<sup>3</sup> healthy adults at high risk of TB,<sup>4</sup> and, according to a preliminary report, in Peruvian children suspected of having *M. tuberculosis* infection or disease.<sup>5</sup> As yet, there are no data on the effect of topical zinc on TST reactivity in individuals living in sub-Saharan Africa.

In addition, we hypothesised that calcipotriol, a topical analogue of 1,25 dihydroxyvitamin D<sub>3</sub> (1,25-[OH]<sub>2</sub>-D<sub>3</sub>) used in the treatment of psoriasis,<sup>6</sup> affects TST reactivity. Vitamin D deficiency is associated with reduced in vivo TST reactivity in experimental TB,<sup>7</sup> and vitamin D supplementation restores TST responses in elderly subjects who are vitamin D deficient.<sup>8</sup> Experimentally, 1,25-(OH)<sub>2</sub>-D<sub>3</sub> induces the production of cathelicidin, a peptide with antimycobacterial properties.<sup>9–11</sup> We therefore investigated the effects of topical calcipotriol and zinc on TST reactivity in children hospitalised with suspected TB.

### MATERIALS AND METHODS

#### Patients

Children admitted to the general paediatric wards at the Chris Hani Baragwanath Academic Hospital,

Johannesburg, South Africa, from March 2009 to September 2012 were eligible for enrolment if they were being investigated for tuberculous infection. Although this is one of the larger departments in Southern Africa, the setting is typical of most public health facilities in the region. Most children admitted to the hospital are aged <5 years and about 20% of admitted children are HIV-infected.<sup>12</sup> Study inclusion criteria included age 6 weeks to 14 years, a radiologically confirmed diagnosis of pneumonia or a clinical suspicion of extra-pulmonary TB, and obtaining the care giver's informed consent. Children were excluded if they were receiving anti-tuberculosis treatment, if a TST had previously been performed or if pre-existing illnesses prevented the application of calcipotriol ointment. Convenience sampling, based on the availability of the study investigators to read the TST at 24 and 48 h, was used to enrol eligible patients. HIV infection was confirmed using DNA polymerase chain reaction in children aged <18 months and by using enzyme-linked immunosorbent assays in older children. Gastric aspirates and TST are performed in children suspected of having *M. tuberculosis* infection. A diagnosis of TB disease, rather than latent tuberculous infection (LTBI), is considered in clinically symptomatic children aged ≤5 years who are TST-positive; these children are routinely given anti-tuberculosis treatment because of the high risk of progression from untreated LTBI to disseminated TB.<sup>13</sup>

The Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa, approved the study (clearance number M080619).

#### *Topical applications*

Zinc sulphate crystals were dissolved in sterile water, then blended into aqueous cream creating a zinc cream containing 2% elemental zinc. Calcipotriol (50 µg/g or 0.005%) was obtained from a commercial supplier (Donovex Cream, Adcock Ingram Limited, Bryanston, South Africa). Aqueous cream was applied over the control TST site. The study was modified after the first 25 children were enrolled, primarily because of concerns about the safety of the topical zinc sulphate cream. Study investigator SGL, who administered the TSTs and applied the topical dressings, noted that a small superficial skin ulcer, about 1–2 mm in diameter, occurred on zinc sulphate cream-covered tests only, even in children with non-reactive TSTs. The ulcer coincided with the site where the TST syringe needle pierced the skin and not over the skin directly overlying the intradermally injected tuberculin solution; the ulcer could be easily distinguished from an indurated TST and did not influence tuberculin measurements. A second batch of zinc cream, made by a different pharmacist using sonication and homogenisation to blend the zinc sulphate

solution into the aqueous cream, produced the same effect on a further six patients. The study was interrupted until a commercially prepared 15% zinc oxide ointment containing 12% elemental zinc (Adminicle Trading, Edenvale, South Africa), which produced no similar ulceration, became available.

#### *Tuberculin skin test administration and reading*

Three separate doses of 0.1 ml RT23 (Statens Serum Institute, Copenhagen, Denmark) containing 2 tuberculin units were injected intradermally (Mantoux method) into the volar surfaces of the right and left forearms of 64 children. Two TSTs were administered in one forearm and one in the other forearm. The skin was anaesthetised by a topical application of EMLA cream (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) at least 60 min before administering TST. All TSTs were performed by SGL using an insulin syringe and needle. A discreet wheal measuring >6 mm in diameter (usually around 9–10 mm in diameter) was evident immediately after the administration of all TSTs, and no TST needed re-injection at another site. The skin surrounding the TST was marked using a black felt-tip marker. Thereafter, each TST was immediately covered with a topical application of aqueous cream, zinc or calcipotriol in a random manner and their placement was recorded. The topical treatments were secured using transparent occlusive dressings. All other study investigators were blinded to the treatments. The TSTs were read by investigators within a 90-min period, 24 and 48 h after TST administration. The TSTs, which can be read after 48–72 h,<sup>14</sup> were definitively read 48 h after administration for convenience.

TSTs were initially categorised as reactive or non-reactive by two groups, each comprising the same two investigators: the first group assessed the first 39 enrolled children and the second group assessed the next 25 enrolled children. Reactive TSTs were categorised as positive or negative. The following study definitions were used:

- 1 Tuberculin reactivity: any skin induration detected by palpation and/or Sokal's 'medium ball-point' method. Transverse diameters of reactive TSTs were measured using the Sokal method<sup>15</sup>
- 2 TST positivity: skin induration ≥10 mm (or ≥5 mm for HIV-infected or severely malnourished children)<sup>16,17</sup>
- 3 TST negativity: skin induration <10 mm (or <5 mm for HIV-infected or severely malnourished children).

The transverse diameter of the indurations was measured to the nearest millimetre using Sokal's method after removal of occlusive dressings and topical applications.

### Statistics

Anthropometric Z-scores were calculated using the World Health Organization (WHO) Anthro and AnthroPlus software programmes (Department of Nutrition, WHO, Geneva, Switzerland). The median anthropometric Z-scores were compared in children with and without positive TSTs using Mann-Whitney tests. The inter-observer agreement for TST reactivity was determined using the kappa ( $\kappa$ ) statistic. The effect of topical calcipotriol and zinc on TST positivity (defined above) was assessed using a  $\chi^2$  analysis of 2x3 contingency tables. Patient-matched measurements of 48 h positive TSTs were compared using the Kruskal-Wallis test. Statistical analyses were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

### Sample size calculation

Based on previous reports showing that topical zinc increases TST reactivity by 32%<sup>4</sup> and TST positivity by 38%,<sup>3</sup> we designed our study to detect a 20% increase in TST positivity rates. A preliminary analysis of 64 patients indicated that our study had 85% power ( $\alpha = 0.05$ ; two-tailed) to detect a 20% difference in TST positivity rates for both control vs. calcipotriol and control vs. topical zinc groups.

## RESULTS

### Demographic characteristics

The median age of the 64 children enrolled was 22 months (interquartile range [IQR] 11 – 49 months); there was no difference in the median ages of the TST-positive and TST-negative children ( $P = 0.9503$ ) (Table 1). Thirty-two (50%) children were male and 18 (28.1%) were HIV-infected. *M. tuberculosis* was cultured from four children (6.3%) and non-tuberculous mycobacteria (NTM) were cultured from another four (6.3%). Two enrolled children died: one was HIV-infected, but both had culture-con-

firmed *M. tuberculosis* disease. Malnutrition was common: 41.4% of the children were underweight for age, 47.1% were stunted and 23.5% had wasting. Nine children were diagnosed with kwashiorkor and three with marasmus (Table 1).

HIV-infected children were less likely to be TST-positive ( $P = 0.026$ ). No TST reactivity was noted in any of the control, calcipotriol or zinc TSTs in any HIV-infected child ( $n = 18$ , including five children who also had kwashiorkor [ $n = 3$ ] or marasmus [ $n = 2$ ]). No TST reactivity was noted in non-HIV-infected children with kwashiorkor ( $n = 6$ ) or marasmus ( $n = 1$ ), children with culture-confirmed *M. tuberculosis* disease ( $n = 4$ ) or in children from whom NTM were isolated ( $n = 4$ ). The anthropometric characteristics are shown in Table 2.

### Tuberculin skin test characteristics

There was very good inter-observer reliability for the presence of TST induration as a binary measure: the  $\kappa$  statistic was 0.90 (95% confidence interval [CI] 0.82 – 0.98) for the first group of 39 children and 0.88 (95%CI 0.80 – 0.97) for the second group of 25.

### Effect of calcipotriol ointment and topical zinc cream on tuberculin reactivity

TSTs were reactive in 15 (23.4%) children, of whom 13 (20.3%) were TST-positive. Topical calcipotriol and zinc induced TST positivity in two children with reactive but negative control TSTs. These treatments, however, but did not induce an induration in those 49 children with non-indurated (i.e., non-reactive) control TSTs (Figure 1). Neither topical calcipotriol nor zinc significantly affected the number of positive TSTs: after 48 h, control and zinc-covered TSTs were positive in 11 (17.2%) children, whereas calcipotriol-covered TSTs were positive in 13 (20.3%) (Figure 2). In reactive TSTs, the median induration size at 48 h was 12.0 mm (25% – 75% IQR 5.0 – 18.0) for the control group, 14.0 (25% – 75% IQR 10.0 – 15.0) for the calcipotriol group and 12.0 (25% – 75% IQR

**Table 1** Demographic data of TST-positive and -negative children\*

	All children ( $n = 64$ ) $n$ (%)	TST-positive ( $n = 11$ ) $n$ (%)	TST-negative ( $n = 53$ ) <sup>†</sup> $n$ (%)	<i>P</i> value
Age, months, median (25 <sup>th</sup> - 75 <sup>th</sup> percentiles)	22.4 (10.9–48.9)	20.8 (14.6–31.9)	23.2 (10.7–56.4)	NS
Sex (% male)	32 (50)	6 (54.5)	26 (49.1)	NS
HIV-infected children	18 (28.1)	0	18 (40.0)	0.026 <sup>‡</sup>
Severe acute malnutrition <sup>§</sup>	13 (20.3)	2 (18.2)	11 (20.8)	NS
Kwashiorkor	9 (14.1)	0	9 (17.0)	NS
Positive <i>M. tuberculosis</i> culture	4 (6.3)	0	4 (7.5)	NS
Positive non- <i>M. tuberculosis</i> culture	4 (6.3)	0	4 (7.5)	NS
Deaths	2 (3.1)	0	2 (3.8)	NS

\*Children were categorised into TST-positive and TST-negative groups according to the indurations measured on the aqueous cream (i.e., controls) covered tests.

<sup>†</sup>49 children with non-reactive TSTs and 4 children with reactive but negative TSTs.

<sup>‡</sup>There were significantly fewer positive TSTs in HIV-infected children (Fisher's exact test).

<sup>§</sup>Defined by the presence of severe wasting (weight-for-length/height Z-score <3) or oedematous malnutrition (kwashiorkor). All children received routine bacille Calmette-Guérin vaccination.

TST = tuberculin skin test; NS = not significant; HIV = human immunodeficiency virus.

**Table 2** Comparison of median anthropometric Z-scores in acutely ill hospitalised children with positive and negative TSTs covered with topical aqueous cream (controls), calcipotriol or zinc\*

	WFA <sup>†</sup>	LFA <sup>†</sup>	WFL <sup>†</sup>
All (n = 64)	-1.70 (-2.57 - -0.87)	-1.82 (-2.68 - -0.51)	-1.18 (-1.96 - -0.36)
Controls			
TST-positive (n = 11)	-0.92 (-1.63 - -0.19)	-0.53 (-1.55 - -0.18)	-1.28 (-1.76 - -0.14)
TST-negative (n = 53)	-1.90 (-2.69 - -1.05)	-2.08 (-2.68 - -0.61)	-1.07 (-1.79 - -0.35)
Calcipotriol			
TST-positive (n = 13)	-1.32 (-2.17 - -0.40)	-0.53 (-2.14 - -0.04)	-1.28 (-1.92 - -0.35)
TST-negative (n = 51)	-1.87 (-2.72 - -1.00)	-2.09 (-2.68 - -0.67)	-1.12 (-1.86 - -0.28)
Zinc			
TST-positive (n = 11)	-1.32 (-1.92 - -0.60)	-0.50 (-1.26 - 0.03)*	-1.38 (-2.13 - -0.26)
TST-negative (n = 53)	-1.88 (-2.69 - -1.00)	-2.10 (-2.69 - -0.69)*	-1.07 (-1.93 - -0.19)

\*Children with positive TSTs were generally heavier and taller than children with negative TSTs, but these anthropometric differences were not significantly different except that for zinc-covered TSTs, children with positive TSTs were taller than children with negative TSTs (\* $P = 0.0350$ ; Mann-Whitney).

<sup>†</sup>Numbers in parentheses represent 25<sup>th</sup> to 75<sup>th</sup> percentiles.

TST = tuberculin skin test; WFA = weight-for-age; LFA = length/height-for-age; WFL = weight-for-length/height.

8.0 – 15.0) for the zinc group. These induration sizes were not significantly different in the three groups ( $P = 0.735$ ; Figure 3).

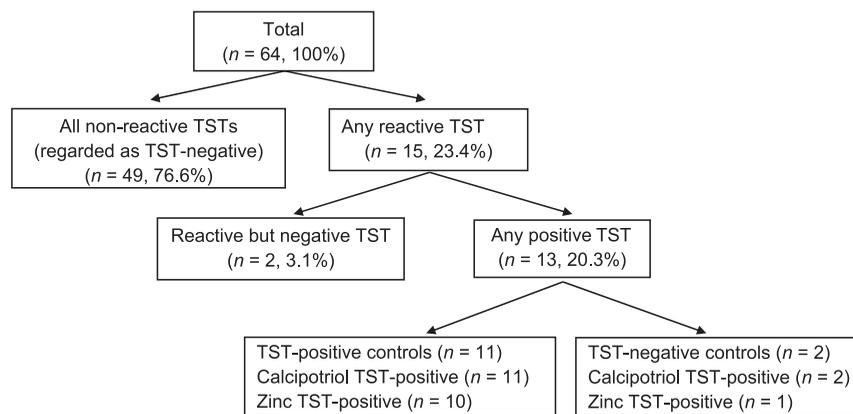
## DISCUSSION

Topical calcipotriol or zinc did not enhance TST reactivity or significantly increase TST positivity rates in hospitalised children investigated for TB in a high TB-HIV disease burden setting, in contrast to previous studies,<sup>3–5</sup> which reported that topical zinc enhances TST reactivity. Specifically, the topical treatments did not assist in the diagnosis of TB in malnourished and/or HIV-infected children, including four children in whom TB was subsequently proven (i.e., culture-confirmed TB disease).

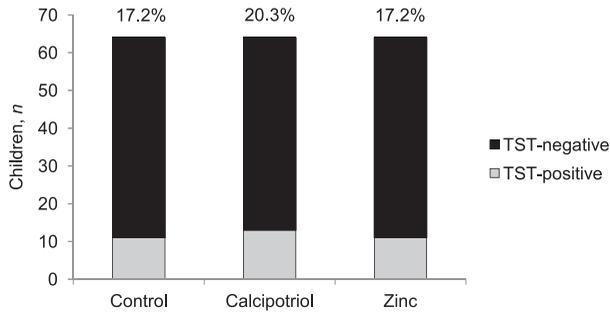
Our failure to measure baseline serum zinc or 25 hydroxyvitamin D levels before enrolment is a major limitation; however, the ineffectiveness of topical calcipotriol or zinc on TST positivity is probably not

due to the confounding effect of oral zinc or vitamin D supplementation. No child with a reactive TST in this study received oral vitamin D supplementation. Oral zinc sulphate was prescribed for nine children with kwashiorkor and four other children with lower respiratory tract infection and co-existing gastroenteritis; none of these children had reactive TSTs. Topical calcipotriol and zinc-induced TST positivity in two children with severe wasting (weight-for-height Z-score < -3). However, the control TST was reactive, but not quite positive (i.e., 4 mm) in one child and reactive at 24 h but not at 48 h in the other child. Furthermore, topical calcipotriol or zinc did not induce *any* TST reactivity in the vast majority of severely malnourished children with non-reactive control TSTs.

Although hypersensitivity responses are suppressed in skin pre-treated with topical vitamin D analogues,<sup>18</sup> we did not observe a suppressive effect of topical calcipotriol on TST reactivity when calcipotriol was



**Figure 1** Study schema showing the effect of topical calcipotriol and zinc on tuberculin skin test (TST) reactivity and TST positivity in a group of 64 acutely ill hospitalised infants in South Africa. TST positivity was defined as  $\geq 5$  mm in malnourished and HIV-infected children and  $\geq 10$  mm in the remaining children. TST negativity was defined as  $< 5$  mm in malnourished and HIV-infected children and  $< 10$  mm in the remaining children. TST = tuberculin skin test; HIV = human immunodeficiency virus.



**Figure 2** The number of hospitalised children with a positive TST (TST positivity rates shown above bars). Each child received three tuberculin tests and the sites of injections were covered with either aqueous cream (control), calcipotriol or zinc cream. Positivity rates were not significantly different in the three treatment groups ( $P = 0.870$ ;  $\chi^2$  analysis of 2x3 contingency tables). TST positivity was defined as  $\geq 5$  mm in malnourished and HIV-infected children and  $\geq 10$  mm in the remaining children. TST = tuberculin skin test; HIV = human immunodeficiency virus.

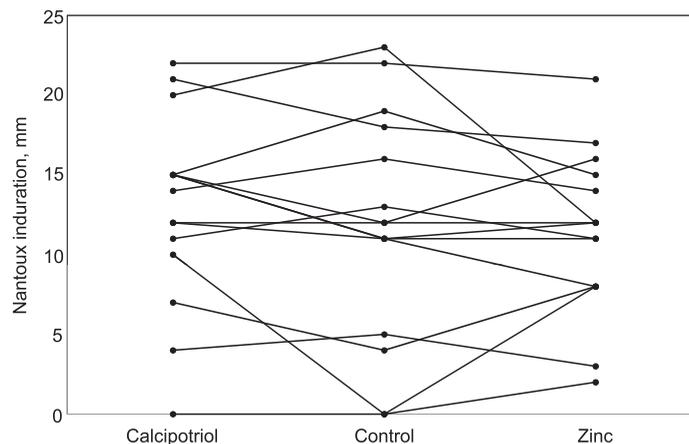
applied to TSTs. We speculate that this is explained by the lack of suppression of epidermal antigen-presenting cell activity by calcipotriol.<sup>19</sup> We further speculate that the children in this study either did not have low zinc levels or that other biological mechanisms drive TST anergy, although topical zinc improves zinc levels in acutely ill, hospitalised children. Zinc oxide may exert a 'weaker' biological effect in contrast to zinc sulphate. Golden et al. reported that zinc oxide is 'virtually insoluble' through the skin,<sup>2</sup> but this may not be true: topical zinc oxide is thought to maintain serum zinc levels in patients receiving total parenteral nutrition,<sup>20</sup> and topical zinc oxide increases epidermal zinc levels in humans.<sup>21</sup>

Our study has other limitations. Although our sample size may have resulted in the failure to detect smaller, but statistically significant, changes in TST induration size, we decided that an improvement of

TST positivity rates by 20% is likely to influence clinical practice. If we assume that our result, which shows a small, non-significant increase in TST positivity rate, is valid, then one additional TST will be positive for every 32 children who receive topical calcipotriol; there were no additional TST-positive tests in the children treated with topical zinc.

In our study, zinc sulphate cream containing a final concentration of 2% elemental zinc induced a small superficial ulcer over the site where the syringe-needle breached the skin, distal to the site of intradermal tuberculin deposition. This superficial ulcer resolved spontaneously without sequelae. We speculate that the presence of undissolved zinc particles in the cream may precipitate a local reaction at the site of the broken skin. However, a second batch of zinc sulphate solution mixed into the aqueous cream carrier using a homogeniser and sonication produced similar results. Alternatively, the ulceration may be due to the higher concentration of zinc sulphate used in this study: local skin effects such as inflammation, swelling and necrosis are described in adults treated with topical zinc sulphate for the therapy of melasma,<sup>22</sup> herpes genitalis<sup>23</sup> and cutaneous leishmaniasis.<sup>24</sup> Despite the widespread use of topical zinc treatments to treat various dermatological conditions in children, safety and efficacy studies are lacking;<sup>25</sup> topical calcipotriol is used to treat psoriasis and is well tolerated, but may cause local irritation.<sup>26</sup> In this study, topical treatments were used in doses much smaller than the recommended therapeutic doses.

Anergic cellular immune responses are most likely to have accounted for the non-reactive TSTs seen in the majority of our study children who had routinely received bacille Calmette-Guérin vaccination at birth. Although we did not use a concomitant control antigen such as *Candida albicans* (which is not available in South Africa), the failure of TST reactivity



**Figure 3** 48 h readings of 15 patient-matched reactive TSTs covered by topical calcipotriol, aqueous cream and zinc. There was no significantly statistical difference when the three patient-matched groups were compared using the Kruskal-Wallis test ( $P = 0.7348$ ). TST = tuberculin skin test.

in children with culture-confirmed *M. tuberculosis* disease suggests that anergic response, rather than non-exposure to mycobacteria, is the main reason for TST non-reactivity in hospitalised children. Two of four children with culture-confirmed *M. tuberculosis* disease were HIV-infected, and we speculate that co-existing severe acute malnutrition (specifically kwashiorkor) and HIV infection contributed to the anergic TST responses in the four children with culture-confirmed *M. tuberculosis* disease.

To control for the potential lack of immunogenic potency of RT23 in a clinical setting, we used unopened, sealed vials of RT23 taken from the same box. As most children were recruited in groups, the same bottle of RT23 was used to administer TSTs to groups of 2–4 children. As 12/14 (85.7%) children with reactive TSTs were given RT23 in this way, we do not believe that the high rates of TST non-reactivity in the other children were due to inert preparations of RT23.

## CONCLUSION

Our preliminary study suggests that topical calcipotriol and zinc do not augment TST responses in acutely ill, hospitalised children. We suggest that further studies should focus on children with severe acute malnutrition who routinely receive standard micronutrient supplementation (which includes zinc, but not vitamin D): significant changes in TST positivity rates, especially if correlated with baseline zinc and vitamin D measurements, will confirm or refute the usefulness of topical treatments on TST positivity in severely malnourished children.

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Conflict of interest: none declared.

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## RESUME

**CONTEXTE :** Le test cutané à la tuberculine (TST) contribue au diagnostic de tuberculose (TB) chez des enfants hospitalisés en phase aiguë. Nous avons recherché l'effet potentialisateur éventuel de crèmes contenant du calcipotriol (analogue de la vitamine D) ou du zinc sur l'induration consécutive au TST.

**MÉTHODES :** Trois TST, l'un effectué sur une zone couverte de crème en phase aqueuse (témoin), le deuxième de crème au calcipotriol et le troisième de crème au zinc, ont été réalisés chez 64 enfants hospitalisés et évalués 24 et 48 h plus tard par des examinateurs ignorant ce qui avait été appliqué sur la zone du test.

**RÉSULTATS :** Les TST se sont avérés réactifs chez 15 enfants (23,4%), dont 13 (20,3%) étaient positifs. Les crèmes au calcipotriol et au zinc ont induit une positivité chez deux enfants dont le TST témoin était réactif mais non positif. Ces traitements n'augmentaient cependant

pas significativement le taux de positivité. Chez les enfants qui avaient des TST réactifs, le diamètre médian de l'induration à 48 h ne mettait pas en évidence de différence significative entre le témoin, le calcipotriol et le zinc qui étaient 12 mm (25–75% IQR 5–18), 14 mm (25–75% IQR 10–15) et 12 mm (25–75% IQR 8–15), respectivement. Ces traitements n'induisaient pas de réactivité ou de positivité du TST chez des enfants présentant une TB confirmée par culture ( $n=4$ ), infectés par le virus de l'immunodéficience humaine ( $n=18$ ) ou atteints de kwashiorkor ( $n=9$ ).

**CONCLUSION :** Le traitement local par calcipotriol ou zinc n'induit pas de réactivité au TST et n'augmente pas significativement le taux de positivité du TST chez des enfants hospitalisés pour une maladie aiguë mais d'autres études sont requises pour évaluer leurs effets chez des enfants gravement malnutris.

## RESUMEN

**MARCO DE REFERENCIA:** La prueba cutánea de la tuberculina (TST) se usa como ayuda al diagnóstico de la tuberculosis (TB) en los niños hospitalizados gravemente enfermos. Se investigó el posible efecto del calcipotriol (un análogo de la vitamina D) o del cinc de intensificación de la induración de la reacción TST.

**MÉTODOS:** Se practicó la TST a 64 niños hospitalizados en tres puntos y se cubrió la zona con crema acuosa tópica (testigo), calcipotriol o cinc. Los investigadores examinaron la reacción a las 24 h y las 48 h, sin conocer el tipo de aplicación local.

**RESULTADOS:** Quince niños presentaron pruebas reactivas (23,4%), de los cuales 13 obtuvieron un resultado positivo (20,3%). El calcipotriol y el cinc tópicos indujeron la positividad de la prueba en dos niños con prueba reactiva pero negativa en el punto de referencia. Sin embargo, estos tratamientos no aumentaron de manera significativa las tasas de

positividad de la reacción TST. En los niños con TST reactiva, la mediana del diámetro de la induración a las 48 h no fue significativamente diferente entre el grupo testigo (12,0 mm; IQR 25%–75% 5,0–18,0) y los grupos tratados con calcipotriol (14,0 mm; IQR 25%–75% 10,0–15,0) o cinc (12,0 mm; IQR 25%–75% 8,0–15,0). Los tratamientos tópicos no indujeron la reactividad ni la positividad de la TST en los niños con enfermedad tuberculosa confirmada por cultivo ( $n=4$ ), infección por el virus de la inmunodeficiencia humana ( $n=18$ ) ni kwashiorkor ( $n=9$ ).

**CONCLUSIÓN:** La aplicación tópica de calcipotriol o cinc no induce reactividad de la TST ni un aumento significativo de las tasas de positividad a la misma en los niños gravemente enfermos y hospitalizados, pero se precisan nuevos estudios que evalúen los efectos de los tratamientos tópicos en la positividad de la reacción a la TST en niños con desnutrición grave.