Effect of Gentamicin Ointment in Patients with Nagashima-type Palmoplantar Keratosis: A Double-blind Vehicle-controlled Study

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Gentamicin ointment has potential in the treatment of Nagashima-type palmoplantar keratosis. However, there is a lack of reliable study data. The aim of this study was to perform a prospective, randomized, double-blinded, contralateral, vehicle-controlled clinical trial. A total of 20 subjects diagnosed with Nagashima-type palmoplantar keratosis by genetic test, who carried nonsense mutations, enrolled in the 30-day study. Gentamicin ointment was applied to the hand and foot on one side of the body, and vehicle ointment was applied to the hand and foot on the other side. The choice of hand and foot in each subject was randomly allocated. The severity of the patient's skin lesions and quality of life were assessed by a blinded evaluator, using the Dermatology Life Quality Index, visual analogue scale scores and digital photography. Gentamicin ointment treatment resulted in a significant improvement in symptoms of hyperkeratosis and foul smell compared with vehicle. No difference was found in the effect on erythema between gentamicin and vehicle. In conclusion, gentamicin ointment demonstrated positive responses and good tolerance in treating Nagashima-type palmoplantar keratosis caused by nonsense mutations.

Key words: Nagashima-type palmoplantar keratosis; read-through; gentamicin.

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SIGNIFICANCE

Nagashima-type palmoplantar keratosis is an autosomal recessive skin disorder characterized by well-demarcated diffuse hyperkeratosis manifesting foul odour and erythema on the palms, feet and Achilles tendon area. Topical emollients and retinoid treatment have limited effects on this disorder. A previous study of 5 patients found that 0.1% gentamicin ointment is effective for Nagashima-type palmoplantar keratosis; however, there is a lack of further study data demonstrating the efficacy of this therapy. The current study of 20 subjects determined the efficacy of gentamicin ointment. The study also compared the efficacy of 0.1% and 0.3% gentamicin ointment, and found no statistical difference between them.

Nagashima-type palmoplantar keratosis (NPPK, OMIM#615598) is an autosomal recessive non-syndromic diffuse palmoplantar keratosis characterized by well-demarcated diffuse hyperkeratosis with redness, extending to the dorsal surfaces of the palms and soles, the flexor aspects of the wrists and ankles, and the Achilles tendon area. Infected sites may also include the elbows and knees. The affected skin shows a white, spongy appearance within 10 min of exposure to water, specifically in the reddish hyperkeratotic area (1). Hyperhidrosis and foul smell are upsetting symptoms that may affect patients' self-confidence from an early age. Hyperkeratosis on the ears and toenail dystrophy have been reported as atypical lesions of NPPK in isolated cases (2, 3). Histological findings include orthokeratotic hyperkeratosis, acanthosis, and hypergranulosis, but epidermolytic hyperkeratosis is not a feature (4).

Kubo et al. (1) identified homozygous or compound heterozygous loss-of-function mutations in *SERPINB7* as a cause of NPPK. SERPINB7, in clade B of the serpin superfamily, is one of the most abundant proteins in the stratum granulosum of skin, and serves as serine protease inhibitor (5). NPPK is the most common form of palmoplantar keratodermas in the East Asian population (1). Assuming a combined null allele frequency of 0.011 and 0.015 in the Japanese and Han Chinese populations, the prevalence rates of NPPK would be 1–2/10,000 and 2–3/10,000, respectively (6). According to the genome Aggregation Database exomes, the allele frequency of c.796C>T(p.Arg266Ter) was 0.7% (125/18,076) in East Asia (gs://gcp-public-data--gnomad Or https://gnomad.broadinstitute.org/). According to the 1000 Genomes Project Phase 3 (http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/) the nonsense mutation c.796C>T(p.Arg266Ter) was carried in a heterozygous manner by 3 of 104 Japanese individuals in Tokyo, 5 of 103 Han Chinese individuals in Beijing, and 2 of 105 in several cities of Southern China, such as Shanghai, Guangdong, et al. Thus, mutation c.796C>T (p.Arg266Ter) is considered to be a founder mutation in the Japanese and Han Chinese populations. This has been confirmed by haplotype analysis in Chinese patients (7). Among the NPPK patients diagnosed by our research team, more than 90% of the

subjects carry the nonsense mutationc.796C>T. With such high frequencies of mutant alleles, the families with NPPK may show pseudodominance.

There is no satisfactory therapy for NPPK, and current treatment, such as topical emollients and keratolytics, produce limited outcomes. One report indicated the potential of topical drugs, such as tacrolimus ointment, because it inhibits T-cell infiltration associated with NPPK pathogenesis (8). However, its long-term safety and curative effect require further observation, and a larger randomized controlled study is needed. Previously, Woodley et al. (9) and Ohguchi et al. (10) used 0.1% gentamicin ointment to treat patients with recessive dystrophic epidermolysis bullosa (RDEB) and patients with NPPK, with good results.

Nonsense suppression therapy has been studied for more than 20 years, and aims to suppress the termination of translation caused by premature termination codons (PTCs) and restore protein function (11). It is important to note that the translational termination by a PTC is not 100% efficient, and decoding of the stop codon by a near-cognate tRNA occurs at a low frequency. This natural suppression of PTCs, so-called "readthrough", can lead to the restoration of a full-length protein (12). Indeed, readthrough induced by aminoglycosides is one of the major nonsense suppression therapies. Some aminoglycosides can bind the A site of the rRNA, which alters the RNA conformation. Moreover, the accuracy between the codon–anticodon pairing is reduced. The decreasing fidelity of the normal translation process results in a misincorporation of near-cognate aminoacyl-tRNAs at the stop codon during the sampling process, which leads to PTC readthrough. Aminoglycosides have minimal effects on normal translation termination, because the normal stop codons of eukaryote genes are surrounded by upstream and downstream sequences, which enhance the efficiency of translation termination, whereas nonsense mutations are usually not surrounded by these sequences (13).

The aim of this study is to evaluate the efficacy and safety of gentamicin ointment in the treatment of NPPK caused by nonsense mutations.

MATERIALS AND METHODS

Population

Patients who were diagnosed with NPPK by genetic test and carried nonsense mutations were recruited to the study, with no restriction on age or sex. Inclusion criteria were: patients with NPPK who were carrying nonsense mutations; and normal results of vital signs. Exclusion criteria were: patients with severe hypersensitivity reaction or who were anergic after sensitization test on the ointment; pregnancy and lactation; abnormal liver and kidney function with clinical significance or hearing loss; and carrying mitochondrial deafness gene. Exit criteria were: patients not willing to undergo treatment and/or regular follow-up; treatment-related adverse reactions or abnormal clinically significant laboratory indicators during the study; voluntary withdrawal of informed consent by the patients; the risks faced by the subjects outweighing the possible benefits of continuing the trial.

Medicines

Gentamicin sulphate (Fukang Pharma, Fujian, China) 0.3% ointment in white petrolatum, gentamicin 0.1% ointment, and ointment vehicle (excipient) were prepared and blinded by Xinhua Hospital Pharmacy.

Study design

This study was designed as a prospective, randomized, double-blinded, contralateral, and vehicle-controlled clinical trial. It was approved by the ethics committee of Xinhua Hospital (approval number XHEC-C-2017-109-2), registered in the Chinese Clinical Trial Register System http://www.chictr.org.cn/showproj.aspx?proj=25169. Registration number: ChiCTR1800014771), and was conducted according to the principles of the Declaration of Helsinki, at the Department of Dermatology of Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine. Informed consent was signed by every participant prior to enrolment.

All patients included in the study were subjected to complete history-taking and a full physical examination. To ensure the safety of the study, some routine laboratory examinations were made, including routine blood tests, blood glucose, renal function tests, liver function tests, routine urine tests, abdominal ultrasound scan, auditory brain stem response (ABR threshold; under 4 years old) and pure-tone threshold (over 4 years old).

Following a safety assessment, a computer-generated randomization list was used to assign one hand and one sole of each patient to the application of 0.3% gentamicin sulphate ointment or 0.1% gentamicin sulphate ointment; and the other hand and sole were assigned to application of vehicle ointment. Both ointments were applied once a day on the lesions for 30 days. One fingertip unit (FTU) of ointment was applied to each 1% of body surface area. Concomitant use of emollients or any topical medicine was not allowed. Follow-up was continued for 3 months to observe the recurrence after discontinuation of the double-blind treatment. Patients were advised to contact the study researchers immediately in case of any unwanted side-effects, including pain or oedema.

Clinical assessments

Before treatment, 4 clinical photographs were taken of each subject, illustrating both sides of the palms and soles. The treatment duration was 30 days. All subjects were scheduled to attend a visit every 10 days: day 0 (baseline), day 10, day 20, and day 30 (end of study). The photographs were taken from the same sides at each visit. The observer was an experienced dermatologist who was blinded to the test medicine. The efficacy of the treatment was assessed by comparing the clinical photographs side by side at baseline and at the end of the study.

The Dermatology Life Quality Index (DLQI) and visual analogue scale (VAS) scores were evaluated at each follow-up visit. The DLQI aims to measure how much the skin problems have affected life in the last 10 days. The intensity is graded on the following scale: 0: none; 1: a little; 2: a lot; and 3: very much. VAS scores from 0 to 10 were used by the participants to assess efficacy through evaluating their skin improvement with regard to hyperkeratosis and erythema. The higher the VAS score, the worse the symptoms.

All adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (https://www.meddra.org/).

End-points

The primary end-point was improvement in hyperkeratosis and erythema compared with the control group. The secondary end-point was improvement in quality of life of patients before and after treatment.

Statistical analysis

Data analyses were performed using statistical software SPSS22.0.0. (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as the mean ± standard deviation (SD). A 2-way analysis of variance (ANOVA) test was used when comparing more than 2 groups of parametric data. Exact *p*-values less than 0.05 were considered statistically significant.

RESULTS

Patients

A total of 20 patients (16 women (80%) and 4 men (20%); mean age 9.1 ± 2.0 years; range 2–35 years) were enrolled in the study. **Table I** shows the patients' characteristics.

There were 10 people in the 0.1% gentamicin group (8 females; 2 males), and 10 in the 0.3% gentamicin group (8 females; 2 males).

Outcomes

The VAS data shows, firstly, that both drug concentration and treatment duration had significant effects on improvement in hyperkeratosis ($p<0.05$) (**Table II**). The improvement in erythema was not obvious after treatment, and there was no significant difference among different concentrations or treatment durations. In addition, analysis of DLQI scores revealed significant differences among different treatment durations ($p<0.05$), but no statistical difference among different drug concentrations ($p>0.05$).

Both of the concentrations of gentamycin have significant improvements in hyperkeratosis compared with the vehicle group ($p<0.05$), but there was no statistical difference between the 2 groups of different concentration of gentamycin ($p>0.05$) (Table SI[1]). Secondly, neither drug concentration nor treatment duration contributed significant variance to the improvement in erythema ($p>0.05$) (Table II). Compared with the vehicle group, the statistical difference was also not significant ($p>0.05$) (Table SI[1]). Finally, the results showed that longer treatment had a better effect on DLQI score ($p<0.05$), but there was no statistical difference between the different concentration groups ($p>0.05$) (Table II).

Table I. Patients' characteristics

Pat. No. (gentamicin ointment concentration)	Sex	Age, years	Mutation (SERPINB7)
P1 (0.1%)	Female	4	c.C796T/c.520_521insT
P2 (0.1%)	Female	13	c.C796T (homo)
P3 (0.1%)	Female	7	c.C796T/c.522dupT
P4 (0.1%)	Female	7	c.C796T (homo)
P5 (0.1%)	Female	2	c.C796T (homo)
P6 (0.1%)	Female	11	c.C796T (homo)
P7 (0.1%)	Male	11	c.C796T (homo)
P8 (0.1%)	Female	2	c.C796T/c.362T>G
P9 (0.1%)	Male	31	c.C796T (homo)
P10 (0.1%)	Female	7	c.C796T/c.522dupT
P11 (0.3%)	Female	3	c.C796T (homo)
P12 (0.3%)	Female	7	c.C796T (homo)
P13 (0.3%)	Male	12	c.C796T/c.522dupT
P14 (0.3%)	Male	3	c.C796T (homo)
P15 (0.3%)	Female	4	c.C796T/c.1106_1107insCAT
P16 (0.3%)	Female	35	c.C796T (homo)
P17 (0.3%)	Female	4	c.C796T/c.336+2T>G
P18 (0.3%)	Female	10	c.C796T(homo)
P19 (0.3%)	Female	2	c.C796T/c.806_818delinsT
P20 (0.3%)	Female	7	c.C796T/c.522dupT

Table II. Comparison (*p*-values) different concentrations of gentamycin ointment and treatment durations in the 2 study groups

	p-value		
	Concentration	Treatment duration	Concentration* duration
DLQI	0.840	<0.001	<0.001
VAS (hyperkeratosis)	<0.001	<0.001	0.148
VAS (erythema)	0.546	0.529	1.000

DLQI: The Dermatology Life Quality Index; VAS: visual analogue scale.

Safety

Comparing the data from laboratory and physical examinations before and after treatment, found no treatment-emergent adverse events (TEAEs). The hand lesion in 2 subjects was exacerbated during treatment, manifesting as erythema, scales, and itching. In addition, these 2 patients both carried a heterozygous *FLG* mutation: c.3321delA/p.Gly1109Glufs, which was identified as being involved in the development of atopic dermatitis (14).

DISCUSSION

NPPK is one of the most common genodermatoses in the East Asian population, and severely affects patients' quality of life. To date, there is no effective treatment. The foul odour resulting from NPPK severely affects the psychological health of young patients, in particular, and can lead to social phobia.

Gentamicin is a well-studied, US Food and Drug Administrations (FDA)-approved antibiotic. Recent *in vitro* and *in vivo* studies have shown that aminoglycoside antibiotics can suppress primary PTCs and produce full-length functional protein in several genetic disorders, such as cystic fibrosis (CF), and Duchenne's muscular dystrophy (DMD) (15, 16). Nevertheless, the clinical use of the aminoglycosides for genetic diseases remains limited, because systemic aminoglycosides have renal and otic toxicities, and they show considerably varying readthrough efficiencies among the target nonsense mutations (9). Vadim et al. (17) and Cogan et al. (18) revealed that gentamicin could restore functional type VII collagen and laminin *β3 in vitro*.

The current study evaluated the efficacy of different concentrations of gentamicin ointment and the safety of the ointment. Both 0.1% and 0.3% gentamicin ointments showed comparable beneficial responses to varying degrees (**Fig. 1**). Clinically, 0.3% gentamicin ointment was

[1]https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3760

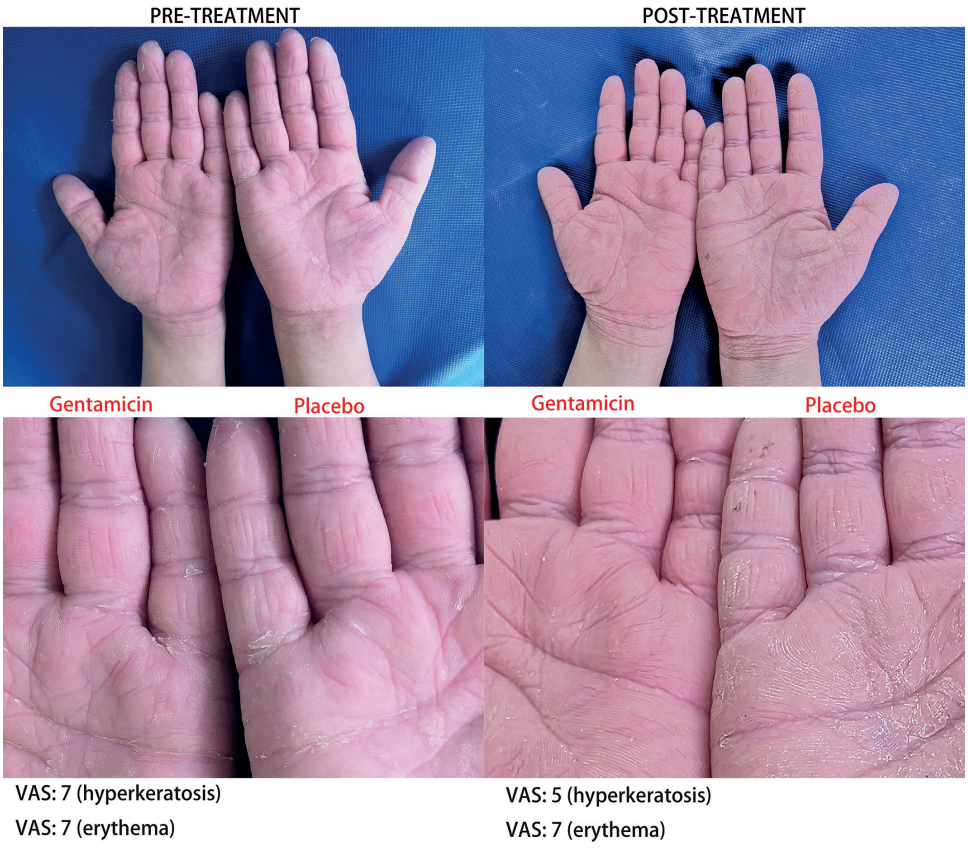

Fig. 1. A participant in the 0.3% gentamicin ointment group. Hyperkeratosis of the gentamicin-treated side improved greatly, while the other side showed limited improvement. The lower row shows the difference between the 0.3% gentamicin ointment and the vehicle before and after treatment. VAS: visual analogue scale score.

more effective than 0.1% with regard to improvement in hyperkeratosis and odour, although the difference was not statistically significant. The improvement occurred mainly in hyperkeratosis and odour, while erythema did not improve. This finding is consistent with the results from Ohguchi et al. (10), who proposed 2 possibilities: (*i*) more synthesis of SERPINB7 is required to completely cure the disease; and (*ii*) some of the gentamicin-induced SERPINB7 may not be fully functional, because aminoglycosides induce ribosomes to readthrough PTCs via the incorporation of random amino acids by near-cognate aminoacyl tRNAs. This view partially explains the outcomes. The improvement in erythema may also be observed after long-term medication. The current study found that 2 adult subjects were far less responsive to the treatment than the children. It is hypothesized that hyperkeratosis of the palm in adulthood forms a hard-shell structure, which can hinder the absorption of drugs. No pathogenic change was observed in renal function, auditory functioning or other laboratory examinations in all the subjects after 30-day treatment. The lesions in 2 subjects were exacerbated during treatment, manifesting as erythema, scales, and itching. Since the hand eczema was concomitant with NPPK, it was assessed as not treatment related. These 2 patients carried a heterozygous *FLG* mutation, and were prone to eczema due to the impaired skin barrier function induced by the heterozygous *FLG* mutation.

Most subjects relapsed after 1-month discontinuation of treatment. It is speculated that the rescued protein functions for only one month in the body. However, the question as to what percentage of physiological SERPINB7 protein level provides reasonable epidermal homeostasis remains to be answered. The gentamicin ointment treatment was repeated for the relapsed patients, and the safety of long-term medication is currently being followed up.

Gentamicin ointment is promising in many genodermatoses, such as epidermolysis bullosa and Hailey-Hailey disease, and is especially suitable in treating NPPK (19). Since the dosage of topical gentamicin used in patients with NPPK is very low, this avoids the systemic absorption caused by large-area application. Moreover, the different stop codons are suppressed with variable efficiencies (in humans, UGA>UAG>UAA), and position +4, the nucleotide following the stop codon, exerts a dramatic influence on the stop fidelity. Adenine ribonucleotide (A) or cytosine ribonucleotide (C) at this position is associated with some of the highest readthrough levels (11). Most of the patients with NPPK carried the TGAA nonsense mutation.

Although treatment with gentamicin ointment benefitted most patients in the study, the effect on 4 patients was not obvious. Nonsense-mediated mRNA decay (NMD) is a conserved eukaryotic surveillance pathway that recognizes and degrades mRNAs containing PTCs (20). The nonsense-mediated mRNA decay (NMD) process plays a

major role in readthrough therapy. Amlexanox, an FDA-approved drug, which was used previously for treatment of mouth ulcers and is currently in in phase II clinical trials for diabetes mellitus type II, has been reported for inhibiting NMD in RDEB patient cells (21). Banning et al. (22) reported that amlexanox was a potential therapy for nonsense mutations in the lysosomal storage disorder aspartylglucosaminuria. It is speculated that a compound preparation consisting of both gentamicin and amlexanox could be more effective than gentamicin alone because the compound provides more PTC-containing mRNA to readthrough than mere gentamicin.

Moreover, this study highlights the specific effects of the active compounds (gentamicin). The use of a true vehicle in clinical studies for topical treatment can be challenging, especially for skin diseases characterized by desquamation and dryness, because any cream applied to the skin may have a moisturizing effect.

The current study has some limitations. It has a relatively low number of participants and short follow-up period. Therefore, a larger sample size and long-term follow-up studies are needed to evaluate the long-term efficacy and safety of the compound preparation in the treatment of NPPK.

In summary, this study represents the largest sample size to date evaluating the efficacy and safety of gentamicin ointment. Moreover, this study compared, for the first time, the efficacy of different gentamicin concentrations. Compared with the control vehicle, gentamicin ointment significantly improved hyperkeratosis, desquamation, and quality of life, based on VAS and DLQI scores. Gentamicin ointment may be a promising treatment for patients with NPPK.

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The data that support the findings of this study are available from the corresponding authors on reasonable request.

The authors have no conflicts of interest to declare.

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