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Efficacy and safety of 'wet-wrap' dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: a critical review of the literature

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Summary

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Conflicts of interest
None declared.

Background During the last two decades wet-wrap treatment (WWT) has been advocated as a relatively safe and effective treatment modality in children with severe and/or refractory atopic dermatitis (AD). Unfortunately, there are still many unsolved issues concerning the use of wet-wrap dressings in patients with AD.

Objectives To make an inventory of the different methodologies and to evaluate the currently available evidence for the use of WWT as an intervention treatment in children with severe and/or refractory AD.

Methods We performed a search of the literature via the online PubMed database. Reference lists from relevant articles were scanned for additional publications. Publications describing a treatment modality for children with severe and/or refractory AD, which included the application of wet dressings, were collected and evaluated using the guidelines of the NHS Centre for Reviews and Dissemination, University of York.

Results Twenty-four publications were included for evaluation. Eleven of the publications detailed original clinical studies (study design level 2–4), while 13 revealed expert opinions (study design level 5). Evidence levels did not exceed level 4.

Conclusions Large prospective studies evaluating the efficacy and safety profile of WWT are lacking. We were able to formulate the following conclusions with a grade C of recommendation. (i) WWT using cream or ointment and a double layer of cotton bandages, with a moist first layer and a dry second layer, is an efficacious short-term intervention treatment in children with severe and/or refractory AD. (ii) The use of wet-wrap dressings with diluted topical corticosteroids is a more efficacious short-term intervention treatment in children with severe and/or refractory AD than wet-wrap dressings with emollients only. (iii) The use of wet-wrap dressings with diluted topical corticosteroids for up to 14 days is a safe intervention treatment in children with severe and/or refractory AD, with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effect. (iv) Lowering the absolute amount of applied topical corticosteroid to once daily application and further dilution of the product can reduce the risk of systemic bioactivity.

The treatment of children with atopic dermatitis (AD) can be challenging for medical professionals as well as for patients and their parents. Conventional treatment, consisting of emollients and topical corticosteroids, is not always sufficient, even when combined with appropriate information and guidance. Recently, topical calcineurin inhibitors have been introduced as an alternative treatment option in children older than 2 years. Although they are a welcome addition to our therapeutic arsenal, they are not more effective than potent topical corticosteroids.[1]

Known intervention treatments for severe and/or refractory AD include systemic corticosteroids, ciclosporin, azathioprine and photo(chemo)therapy.[2–5] All of these interventions have their potential side-effects and (relative) contraindications, especially in children. During the last two decades wet-wrap treatment (WWT) has been advocated as a

relatively safe and effective treatment modality in children with severe and/or refractory AD. Despite several publications from different research groups, there are still many unsolved issues concerning the use of wet-wrap dressings in the treatment of AD. We performed a review of the literature in order to make an inventory of the different methodologies and to evaluate the currently available evidence for the use of WWT as an intervention treatment in children with severe and/or refractory AD.

Materials and methods

Review questions

The following review questions were drawn up based on a population of children with severe and/or refractory AD. WWT was defined as a treatment modality using a double layer of tubular bandages or gauze, with a moist first layer and a dry second layer.

1 In which ways does the methodology of the treatment with wet-wrap dressings differ between the publications?

2 Is the use of wet-wrap dressings an efficacious intervention treatment modality?

3 Is the use of wet-wrap dressings with (diluted) topical corticosteroids more efficacious than the use of wet-wrap dressings with emollients or emollients in combination with antiseptics?

4 Is the use of wet-wrap dressings with (diluted) topical corticosteroids a safe intervention treatment modality?

Literature search

We performed a search of the literature via the online PubMed database. Different search strings were entered using the keywords 'wet-wrap' and 'wet dressings' alone or in combination with 'atopic dermatitis' and 'atopic eczema'. Reference lists from relevant articles were scanned for additional publications. Publications describing a treatment modality for children with severe and/or refractory AD, which included the application of wet dressings, were collected. The publications were then divided according to primary study design hierarchy as described in the guidelines of the NHS Centre for Reviews and Dissemination, University of York (level 1–5).[6] With regard to the review questions concerning effectiveness, we also assessed the quality of the publications and assigned a level of evidence (level 1–5), which led to grades of recommendation attached to the conclusions.

Results

Twenty-five publications were collected after our search was performed. Twenty-four of these publications were included for evaluation. Eleven of the included publications detailed original clinical studies (study design level 2–4),[7–17] while 13 revealed expert opinions (study design level 5).[18–30] One original clinical study was performed in infants with moderate AD and was thus excluded from the Results section.[31] Because of the unique nature of this last study, it will be discussed briefly further on. The publications with expert opinions showed some overlap in content, caused by multiple publications from the same author or institution.

In which ways does the methodology of the treatment with wet-wrap dressings differ between the publications?

The methodology of WWT, as described in the 24 publications, differs with regard to nine key points, as is summarized in Table 1. If we look only at the clinical studies, we find that 10 of the 11 advocate the application of either cream ($n = 6$) or ointment ($n = 4$) directly on the skin instead of soaking the first layer of bandages in warmed-up cream ($n = 1$). When mentioned, the primary reason for direct skin application is that it would be less time consuming. (Re)wetting of the first layer of bandages was carried out with plain water in 9 of these 10 studies and was combined with an aqueous solution of chlorhexidine in one. With the exception of one publication, describing a facial WWT with plain gauze, all the clinical studies reported the use of elasticated tubular cotton bandages. In studies they used Tubifast®, while in one study they used Tubegauz® and in another study either Tubifast® or Tubigrip®, depending on the preference of the patients and their parents. Four of the 11 studies reported a WWT including a facial mask.

Table 1 Possible differences in the methodology of wet-wrap treatment

Topical product	Cream or ointment as emollients, (diluted) topical corticosteroids or a combination of both
Type of bandages	Double layer of cotton cloth, plain cotton gauze or elasticized cotton tubular bandages (Tubigrip®, Tubegauz® or Tubifast®). A second layer of flannel instead of cotton was also reported
Application technique of topical product	The topical product is applied directly on the skin or is warmed up and used to soak the first layer of bandages, which is then applied on to the skin
Application frequency of topical product	Once to thrice daily
(Re)wetting of the first layer of bandages	Once, twice, thrice or every 2–3 h daily. Water is most commonly used but an antiseptic solution and soaking of the first layer in heated cream have been reported
Bandages left in situ	3, 6–8, 12 or 24 h day^{-1}
Area treated	Only the extremities, the trunk and the extremities, only the face, or the entire body
Duration of treatment	Intervention treatment of 2–14 days
Location of treatment	Hospitalization or outpatient treatment

Is the use of wet-wrap dressings an efficacious intervention treatment modality?

Ten of 11 original clinical studies included reported data on the efficacy of a WWT in children with severe and/or refractory AD. They all used a WWT consisting of a double layer of tubular bandages or gauze, with a wetted first layer and a dry second layer. Cream or ointment was applied directly on the skin in nine studies and soaked into the first layer of bandages in the study of Goodyear et al.[9] The details concerning the patient population, topical products, application frequency, duration of treatment and outcome parameters of efficacy are listed in Table 2.

Efficacy was scored using different clinical scoring systems. The SCORAD index was used in one publication. This system combines the extent (A) and intensity (B) of skin lesions with subjective scores on itch and sleeplessness.[32] Three publications used the modified objective SCORAD (A and B) and one publication used a regional SCORAD (B). Unclassified clinical scoring systems were used in two and investigator global assessment in three studies. Additional parameters included transepidermal water loss measurement, parental questionnaires aimed at the subjective assessment of the impact of AD on daily life and similar patient or parent assessments obtained during an interview.

Although the methodology varied with regard to several other previously mentioned key points, all studies reported a successful intervention treatment of 2–14 days, with an improvement of AD skin lesions (evidence level 4). This is in concordance with the stated expert opinions and our own experiences, which describe WWT as a successful intervention treatment in children with severe and/or refractory AD (evidence level 5).

Is the use of wet-wrap dressings with (diluted) topical corticosteroids more efficacious than the use of wet-wrap dressings with emollients or emollients in combination with antiseptics?

Several experts describe a successful WWT with emollients only, usually in patients with milder but still extensive skin disease.[18–20,22,28,29] However, WWT using (diluted) topical corticosteroids is generally regarded as being more efficacious, which is in concordance with our own experiences (evidence level 5). The available data from the two clinical studies detailed below supports this notion, although the number of patients included is small (evidence level 4).

Schnopp et al.[14] reported a controlled trial in which they performed a WWT on both arms of 20 patients. They used mometasone furoate (MF) 0·1% ointment on one side and its vehicle on the other side. After 3 and 5 days the severity of AD lesions improved on both sides, with a significantly better improvement of the regional SCORAD scores on the MF-treated sides compared with the vehicle-treated sides.

Wolkerstorfer et al.[17] performed a pilot study on the influence of corticosteroid dilution on the efficacy of WWT. They report an impressive improvement in the modified objective SCORAD scores after 1 week of treatment, irrespective of the dilution of fluticasone propionate (FP) 0·05% cream used (5%, 10% or 25%). Two patients were treated with the same methodology, using emollients instead of diluted FP cream. They showed only a minor improvement. The improvement in objective SCORAD scores in their study was related to the absolute amount of corticosteroid applied per m^2 body surface. This curve levelled out at approximately 800 $\mu g\ m^{-2}$ body surface, above which efficacy hardly increased further.

No statements can currently be made on the efficacy of a WWT using emollients and antiseptics compared with (diluted) corticosteroids or emollients alone. Abeck et al.[7] published a clinical study detailing a WWT with application of emollients thrice daily combined with chlorhexidine 0·5% solution twice daily to wet the first layer of bandages. Their treatment was efficacious, showing an improvement of the SCORAD index from 56·9 (± 5·6) to 32·4 (± 1·5) after 3 days of treatment (evidence level 4). However, a direct comparison of these results with studies using (diluted) corticosteroids or emollients alone is not possible due to differences in methodology and outcome measures.

Is the use of wet-wrap dressings with diluted topical corticosteroids a safe intervention treatment modality?

When using wet-wrap dressings with (diluted) topical corticosteroids the primary safety concern is systemic bioactivity of the corticosteroids. Six of the clinical studies included safety parameters intended to detect systemic bioactivity, as detailed in Table 3.

Measurements of early morning serum cortisol (EMSC) and urinary cortisol/creatinine ratio before and after treatment have shown a temporary decrease of the values during treatment periods of 2–14 days (evidence level 4). Goodyear et al. found profound decreases of EMSC levels to below the detection level in all their patients after 2–5 days of treatment.[9] Two weeks after completion of the active therapy their values had normalized. The publications of Wolkerstorfer et al.[17] and Devillers et al.[8] showed that the risk of EMSC levels dropping below the lower reference value could be decreased by once daily application and further dilution of the topical corticosteroids to 10% or even 5% of their original strength (evidence level 4). Prolonged suppression of the hypothalamus–pituitary–adrenal cortex axis has not been reported after short-term intervention treatment. Devillers et al.[8] reported one adult patient with a prolonged suppression after a long-term treatment at home, with an average follow-up of 17 weeks (range 11–41). He also used concomitant corticosteroids via inhalation.

One of the most important clinical symptoms of systemic bioactivity of corticosteroids in children is growth retardation. McGowan et al.[11] looked at short-term growth and bone turnover during WWT with diluted corticosteroids in eight children with a median age of 5·1 years (range 3·3–8·8). They used knemometry to measure lower leg length growth rate and urinary deoxypyridinoline crosslink excretion corrected for creatinine excretion to measure bone and collagen

Table 2 Clinical studies on the efficacy of wet-wrap treatment

First author	Study design	Patients	Topical product	Application	Duration	Efficacy
Abeck[7]	Observational	3 children (3–12 years) 3 adults	Emollients and chlorhexidine solution	3 dd 2 dd	24 h day^{-1} 3 days	SCORAD index
Devillers[8]	Observational; inpatient comparison	14 children (6 months–10 years) 12 adults	Diluted (5–25%) FP cream	1 dd	24 h day^{-1} 6–9 days	Modified objective SCORAD
Goodyear[9]	Observational	30 children (9 months–2 years)	HCA 0·5% cream (< 2 years) Diluted (10%) BV cream (> 2 years)	2 dd 2 dd	24 h day^{-1} 2–5 days	IGA
Mallon[10]	Observational	21 children (4 months–10 years)	HCA 0·5% cream (< 2 years) Diluted (10%) BV cream (> 2 years)	1 dd 1 dd	24 h day^{-1} Up to 5 days	IGA and parental questionnaire
Oranje[12]	Observational	3 children (6 months–4 years) 4 adults	Diluted (50%) FP cream	1 dd	24 h day^{-1} 14 days	Modified objective SCORAD
Pei[13]	Randomized controlled	40 children (1–15 years)	Diluted (10%) FP ointment vs. diluted (10%) MF ointment	1 dd 1 dd	8 h day^{-1} 14 days	CSS and parental questionnaire
Schnopp[14]	Randomized controlled; inpatient comparison	20 children (2–17 years)	MF ointment vs. vehicle	2 dd 2 dd	16 h day^{-1} 5 days	Regional SCORAD and TEWL
Tang[15]	Observational	12 children (3–12 years)	Diluted (10–15%) MF ointment	1 dd	12 h day^{-1} 14 days	CSS and self-assessment
Tang[16]	Observational	10 children (4–15 years)	Diluted (10%) MF ointment	1 dd	3 h day^{-1} A few days	IGA and parental assessment
Wolkerstorfer[17]	Observational; comparison	31 children (5 months–13 years)	Diluted (5–50%) FP cream	1 dd	24 h day^{-1} 14 days	Modified objective SCORAD

FP, fluticasone propionate; HCA, hydrocortisone acetate; BV, betamethasone valerate; MF, mometasone furoate; dd, times per day; IGA, investigator global assessment; CSS, unspecified clinical scoring system; TEWL, transepidermal water loss.

Table 3 Clinical studies into the safety of wet-wrap treatment with (diluted) topical corticosteroids

First author	Study design	Patients	Topical product	Application	Duration	Safety
Devillers[8]	Observational; inpatient comparison	14 children (6 months–10 years)	Diluted FP cream	1 dd	24 h day^{-1}	Early morning serum cortisol
		12 adults			6–9 days	
Goodyear[9]	Observational	30 children (9 months–2 years)	HCA 0·5% cream (< 2 years)	2 dd	24 h day^{-1}	Early morning serum cortisol
			Diluted BV cream (> 2 years)	2 dd	2–5 days	
McGowan[11]	Observational	8 children (3·3–8·8 years)	Diluted BD	1 dd	24 h day^{-1}	Knemometry and urinary deoxypyridinoline crosslink excretion
					Up to 14 days	
Oranje[12]	Observational	3 children (6 months–4 years)	Diluted FP cream	1 dd	24 h day^{-1}	Early morning serum cortisol
		4 adults			14 days	
Tang[15]	Observational	12 children (3–12 years)	Diluted MF ointment	1 dd	12 h day^{-1}	Early morning serum cortisol
					14 days	
Wolkerstorfer[17]	Observational; comparison	31 children (5 months–13 years)	Diluted FP cream	1 dd	24 h day^{-1}	Early morning serum cortisol and urinary cortisol/creatinine ratio
					14 days	

FP, fluticasone propionate; HCA, hydrocortisone acetate; BV, betamethasone valerate; BD, beclomethasone dipropionate; MF, mometasone furoate; dd, times per day.

Table 4 Reported complications, besides temporary systemic bioactivity, during an intervention treatment with wet-wrap dressings and (diluted) topical corticosteroids for a maximum period of 14 days

Adverse event	Occurrence
Discomfort, including chills and poor acceptance	Frequent
Folliculitis	Common
Refractory skin lesions on the areas not covered by bandages	Common
Impetigo	Rare
Cutaneous *Pseudomonas aeruginosa* infection	Rare
Herpetic infections	Rare

turnover. There were no significant differences found between the outcomes before and during a median treatment period of 12 weeks (range 2–18).

Table 4 lists reported adverse events other than systemic bioactivity in both clinical studies and expert opinions. Unfortunately only four of the 11 clinical studies report percentages on some of these adverse effects.[8–10,15] We decided to assign each event to a different risk factor group, stating the frequency as rare, common or frequent. The assignments were made on the basis of the limited available data on percentages and on our own personal experience.

Discussion

This review confirms our initial suspicion regarding the wide variety in methodology with regard to WWT. Based on the available data and our own experiences we would like to make some general remarks with regard to future standardization of treatment.

Most authors, including ourselves, advocate application of cream or ointment directly on the skin instead of soaking the first layer of bandages in heated cream. Preparation time can thus be reduced, while good efficacy is maintained. Application frequencies of up to three times per 24 h have been reported during use of emollients. Using diluted topical corticosteroids is more efficacious than using emollients only. However, using diluted topical corticosteroids warrants once daily application, because of the risk of systemic bioactivity. Which topical corticosteroid should be used and to what degree it should be diluted is still uncertain. The most commonly reported products used are 10% dilutions of potent corticosteroids.[9,10,13,15,16] The studies from Wolkerstorfer *et al.*[17] and Devillers *et al.*[8] confirmed a good clinical efficacy and safety of WWT using a 10% dilution of FP cream. They also reported good results with a 5% dilution, which might indicate that further dilution without loss of efficacy is possible. At this moment a 10% dilution seems to provide adequate efficacy and safety and is a good starting point for further studies. Advocating the use of FP or MF above other moderately potent corticosteroids is based on their known pharmacological properties and is another issue in need of further investigation.

In theory, all close-fitting cotton bandages can be used in WWT. Tubifast® elasticated tubular cotton bandages are currently the most commonly used. In 2003 Tubifast Garments® were introduced on to the market. This product line includes long-sleeved shirts, pants, socks and gloves in different paediatric sizes. They are made from similar material as the original Tubifast® and can be washed and reused up to 20 times according to the manufacturer. Using the garments facilitates the treatment and may save a considerable amount of time during the preparation and application phase of the treatment. The use of a facial mask during a WWT is possible and can have good clinical results.[8,12,16,17] However, one should always keep in mind the psychosocial consequences of wearing a mask and the fact that not all children and/or parents will accept their application. Their use should be discussed separately with patients and their parents when WWT is considered.

Different strategies were reported regarding application time of the bandages, ranging from 3 to 24 h daily. Longer application times are probably more efficacious, although there is no clear evidence to support this. In a hospital setting a 24-h treatment schedule is feasible and in our opinion advisable. This is more difficult when patients are treated on an outpatient basis and schedules have to be incorporated into daily life. Intervention treatments of 2–14 days have been published in clinical studies. With use of (diluted) topical corticosteroids, we would like to advocate an intervention treatment with a maximum of 7 days. This period is consistent with the study of Wolkerstorfer *et al.*,[17] who reported substantial improvement during the first week of treatment with little further improvement in the second week, and with the strategy of most authors, who describe good clinical efficacy with treatment periods of up to 1 week (Table 2).

Wet-wrap treatment, especially when combined with (diluted) topical corticosteroids, is a very efficacious intervention treatment in children with severe and/or refractory AD. Unfortunately it is also a very laborious and time-consuming treatment modality that calls for close supervision. Use of topical corticosteroids involves the risk of systemic bioactivity, and the different parameters influencing this risk should be considered. Several possible risk factors for systemic bioactivity during WWT with diluted corticosteroids were suggested, including the type of corticosteroid, the dilution, twice daily vs. once daily application, interindividual differences between patients and the use of concomitant corticosteroids, for instance via inhalation. Four of the six clinical studies summarized in Table 3 propagated the use of a 'new generation' topical corticosteroid, either FP or MF. These products claim a potent local effect with relatively low systemic absorption, which in theory should be beneficial for further reduction of systemic bioactivity during WWT with diluted corticosteroids. However, a controlled trial comparing the use of these products vs. the older topical corticosteroids in a WWT is lacking.

Other adverse events are usually mild and temporary but should also be considered. The reported discomfort is mostly due to chills after application of the first moist layer of bandage, warranting close attention to the temperature of the water. Induction of folliculitis is probably due to the occlusive effect of the treatment and may be reduced by using creams instead of ointments and application of the topical product in the direction of hair growth. Whether or not there is an increased risk of impetigo or herpetic skin infections is still unclear. Both events are well-known complications in children with AD without WWT. Secondary skin infections with *Pseudomonas aeruginosa* appear to be rare, but are possibly due to the moist environment induced by the bandages. Insufficient cleaning of the water sprayers used to rewet the first layer of bandages may constitute a cause of infection. Although striae have not been reported during a wet-wrap intervention treatment, they were observed during a long-term intermittent treatment.[8] Because children entering puberty are already at risk of developing striae, we consider this age group to have a relative contraindication against WWT. Cost-benefit ratios of WWT were not included in this review, but seem to be lacking at the moment.

We believe that WWT should be reserved for second-line intervention treatment in patients with AD who have failed to respond to conventional treatment schedules. This is in concordance with a publication from Goodyear and Harper, who advocated caution in the use of WWT for AD.[21] Further support is found in a recent publication from Beattie and Lewis-Jones, who performed a pilot study comparing a WWT with hydrocortisone acetate cream with the use of hydrocortisone acetate cream twice daily without wet-wrap dressings.[31] Both patient groups consisted of children with moderate AD. No significant differences in clinical efficacy scores or quality of life scales were found between the two groups and the authors concluded that WWT should not be considered as a first-line treatment in mild to moderate AD.

This review shows an overview of the currently available evidence for the use of WWT as an intervention treatment in children with severe and/or refractory AD. Although the reported clinical studies started with a study design ranging from level 2 to level 4, the resulting evidence levels did not exceed level 4. This was mostly due to the small numbers of patients included, which together with the different methodologies of the clinical studies form the main weakness of this review. Presently we need large prospective studies to evaluate the efficacy and safety profile of WWT as an intervention treatment in children with severe and/or refractory AD. In addition to standardized clinical efficacy and safety parameters, these studies should also include quality of life assessments and cost-benefit ratios as outcome parameters. These studies are necessary for further standardization of the methodology and should focus on the use of diluted topical corticosteroids vs. emollients and the comparison of WWT with more conventional treatment modalities.

Recommendations

Based on the available data we were able to formulate the following conclusions with a grade C of recommendation.

1 Wet-wrap treatment using cream or ointment and a double layer of cotton bandages, with a moist first layer and a dry second layer, is an efficacious short-term intervention treatment in children with severe and/or refractory AD.

2 The use of wet-wrap dressings with diluted topical corticosteroids is a more efficacious short-term intervention treatment in children with severe and/or refractory AD than wet-wrap dressings with emollients only.

3 The use of wet-wrap dressings with diluted topical corticosteroids for up to 14 days is a safe intervention treatment in children with severe and/or refractory AD, with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effect.

4 Lowering the absolute amount of applied topical corticosteroid to once daily application and further dilution of the product can reduce the risk of systemic bioactivity.

We would like to stress that the success of WWT depends on adequate training of patients and parents in the methodology of the treatment. In our opinion a skilled dermatological nurse is invaluable in this process.

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