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Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms

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Summary

We performed a randomized double-blind study within-group comparison in 11 patients to study the effect of subcutaneous injections of botulinum A toxin in focal hyperhidrosis of the palms. A total dose of 120 mU (mouse units) of botulinum A toxin (Dysport®) was injected into six different sites on one palm, whereas the other was injected with sterile saline. Objective quantification of sweat production was performed using digitized ninhydrin-stained sheets. Three weeks after treatment, the mean reduction of sweat production in the botulinum A toxin-treated palms was 26% ($P < 0{\cdot}001$), after 8 weeks 26% ($P = 0{\cdot}002$) and after 13 weeks 31% ($P < 0{\cdot}001$). Subjective assessment of sweat production by the patients using a visual analogue scale showed a 38% improvement in the botulinum A toxin-treated palms at 3 weeks ($P = 0{\cdot}002$), 40% at 8 weeks ($P = 0{\cdot}002$) and 38% at 13 weeks ($P = 0{\cdot}002$). Neither the objective measurement nor the subjective rating showed a statistically significant reduction of sweating in the placebo-treated palms. Three patients reported reversible minor weakness of powerful handgrip after injection at the toxin-treated site, lasting between 2 and 5 weeks.

Research has transformed botulinum toxin from a dangerous and feared poison to an important drug for the improvement and occasional cure of conditions that were previously difficult to treat.[1] Botulinum A toxin acts primarily at peripheral cholinergic synapses, inhibiting the release of acetylcholine. Its therapeutic effect is mainly due to its action on the neuromuscular junction, where it causes transient paresis in the muscles into which it is injected.[2,3]

Local injection of botulinum A toxin has been established as the treatment of choice for cranial and cervical dystonias and related disorders.[2–5] Ophthalmologists now use botulinum A toxin to treat squint and other ocular motility disturbances and there is a steadily increasing range of new or potential indications in other fields, such as paediatrics, otorhinolaryngology, rehabilitation medicine, plastic and cosmetic surgery, gastroenterology and urology.[1,6–10] Side-effects after local injection of botulinum A toxin are usually mild and due to weakness in the injected muscles and those surrounding them,[2–4] but subclinical side-effects on the cholinergic synapses of the autonomic nervous system have also been reported.[11–14]

Recently there have been suggestions for potential clinical indications in non-muscular diseases where cholinergic terminals play a part.[15–18] Thirteen patients with gustatory sweating (Frey's syndrome) were effectively treated with botulinum A toxin[15,16] and subcutaneous injection of botulinum toxin into the dorsum of the hands and axillae of three healthy volunteers were recorded as having resulted in circular areas of complete anhidrosis.[17] In self-experiments we showed that botulinum A toxin has a potent inhibiting effect on the cholinergically innervated sweat glands on the palms, leading to marked reduction in sweat production.[18]

Here we report on a randomized double-blind study within-group comparison in 11 patients, which demonstrates the clinical efficacy of botulinum A toxin as an antihidrotic agent with prolonged action.

Materials and methods

Patients

Eleven patients [seven male, four female, aged 23–54 years (mean: 33·2 ± 9·6 SD)] were included in the trial. All patients were resistant to any conventional treatments and were socially handicapped by palmar hyperhidrosis. We excluded patients younger than 18 years of age, pregnant women and patients with systemic

diseases that cause hyperhidrosis. Hyperhidrosis had been present since early childhood in 10 patients and in one for 3 years following major head trauma. Procedures and follow-up visits were carried out on an outpatient basis. The study was approved by the Ethics Committee of the Medical Faculty of the University of Vienna. Informed consent was obtained from all patients after a full written and oral explanation.

Study design

The study was designed as a randomized, double-blind, placebo-controlled trial within-group comparison. All patients underwent a pretreatment evaluation consisting of clinical assessment, objective quantification of sweat production and subjective rating of the individual sweating profile. The patients were randomly assigned to receive a total dose of 120 mU (mouse units) of botulinum A toxin (Dysport®) at six different sites into one palm, whereas the other was injected with normal saline in the same fashion. Both the patients and the physician giving the injections were unaware of the treatment side. Objective quantification of sweat production was performed 3, 8 and 13 weeks after treatment. The observation period of 13 weeks was chosen because the therapeutic effects of botulinum A toxin in patients with dystonias last for an average of 8–12 weeks.[3,6] The code was broken in all cases after 13 weeks.

Subcutaneous injection of botulinum A toxin

Before treatment, cold packs (Flexum®) were placed on both palms for 30 min to minimize the pain of the injections. The total dose of 120 mU botulinum A toxin (Dysport®, diluted with 0·5 ml of 0·9% sterile saline), was injected subcutaneously into one palm at six different sites (i.e. 20 mU per site) using a gauge needle (G26 × 1/2, 0·45 × 1/2). The other palm was injected with sterile saline without any toxin.

Objective measurement

Ninhydrin sweat tests on both palms were performed before and 3, 8 and 13 weeks after botulinum A toxin injections in a room with constant temperature at 22°C and relative humidity at 65%.[19] An objective quantification of sweat production was performed using digital image analysis. The ninhydrin-stained sheets were digitized and transferred on to an IBAS 2000 image analysis workstation (Zeiss-Kontron, Germany). The amount of stained area was counted using a standardized algorithm. Measurements were carried out in a blinded fashion by one skilled investigator and image measurement, which showed excellent reproducibility, was performed twice. In one patient (no. 11) the ninhydrin test sheets could not be analysed due to technical problems in the staining reaction.

Subjective rating

All patients were asked to complete questionnaires recording their subjective impression of sweat production before and after treatment with botulinum A toxin at weekly intervals. The patients were asked to quantify the intensity of sweat production using a visual analogue scale (VAS) of 100 points for both the right and left palm (0 = no sweating, 100 = the most severe sweating). Side-effects were documented by a structured check-list attached to the questionnaire.

Statistical analysis

All the statistical analyses were performed according to the intention to treat principle. Baseline characteristics measured on a nominal or an ordinal scale were compared by χ^2 procedures. Continuous measures were compared by using paired and unpaired *t*-tests as appropriate. Statistical analyses were two-sided, with an α-error of 0·05. SPSS (SPSS 6·0, Chicago Illinois, 1993) software was used for all analyses.

Results

Comparison of baseline values

No substantial differences were found at baseline between the botulinum A toxin-treated palm and the untreated one. Using the morphometric measurements, the difference in pixels at baseline between the two palms was about 1% ($P = 0·91$). The same was true for the subjective impression of the patients using the VAS.

Objective rating

Three weeks after initiation of treatment the mean reduction in sweat production in the botulinum A toxin-treated palms was 26% (95% confidence interval 13%–39%, $P < 0·001$), after 8 weeks 26% (95% confidence interval: 11%–42%, $P = 0·002$) and after 13 weeks 31% (95% confidence interval: 20%–42%,

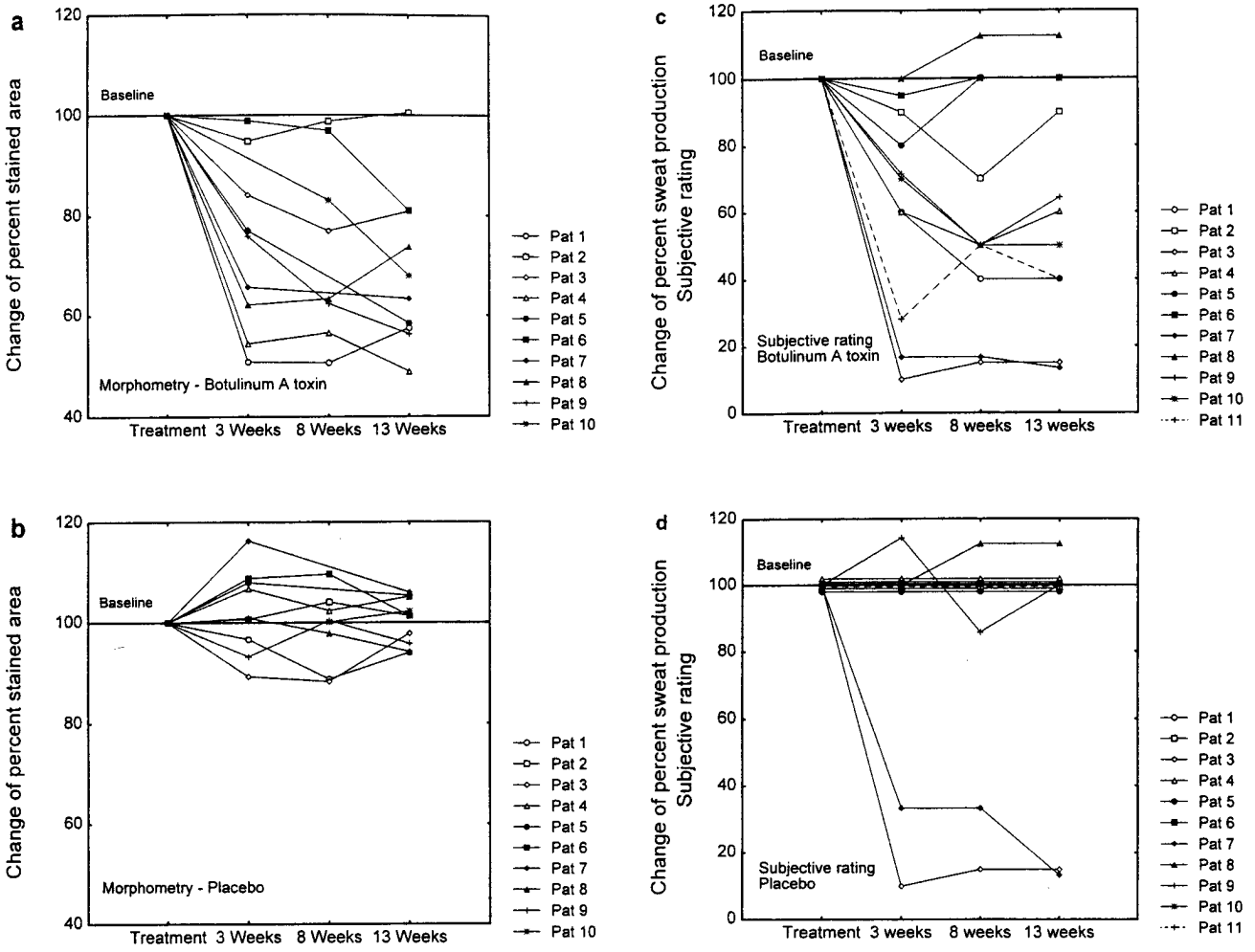

Figure 1. (a) Sweating after botulinum A toxin treatment (objective measurement). The line graph shows the relative change in sweat production over time as assessed by digital image analysis of ninhydrin test sheets. In nine of 10 tested individuals a substantial decrease in sweat production is demonstrated. (b) Sweating after placebo treatment (objective measurement). The line graph shows the relative change in sweat production over time as assessed by digital image analysis of ninhydrin test sheets. No significant change of sweat production could be demonstrated. (c) Sweating after botulinum A toxin treatment (subjective rating). The line graph shows the relative change in sweat production over time as recorded by visual analogue scale (VAS). (d) Sweating after placebo treatment (subjective rating). The line graph shows the relative change in sweat production at the placebo site over time as recorded by VAS.

$P < 0{\cdot}001$) (Fig. 1a). In the placebo-treated palm, mean changes were statistically not significant and varied from 0·2% to 1·2% (Fig. 1b).

Subjective rating (VAS)

Three weeks after initiation of treatment, the subjective mean improvement in sweat production in the botulinum A toxin-treated palms was 38% (95% confidence interval 17%–59%, $P = 0{\cdot}002$), after 8 weeks 40% (95% confidence interval: 18%–63%, $P = 0{\cdot}002$) and after 13 weeks 38% (95% confidence interval: 16%–61%, $P = 0{\cdot}002$). In the placebo-treated palm, no statistically significant subjective improvement was found at any of the time points.

Subjective rating revealed a beneficial effect, lasting for the entire observation period, in eight of 11 patients at the toxin-treated site (Fig. 1c). Two additional patients experienced only mild and shortlasting reduced sweat production at the toxin-treated site. Interestingly, two patients with excellent response at the treated site also experienced substantial relief on the placebo-treated palm (Fig. 1d).

Side-effects

Three patients reported transient minor muscle weakness after injection at the toxin-treated site, lasting between 2 and 5 weeks. Two of them reported on quicker fatigue while, for example, tying up laces and

hairdrying whereas another experienced only 'a feeling of numbness' at the toxin-treated site. One patient reported minor haematomas at the injection sites. Whereas eight patients did not note any difference between botulinum and saline injections, three patients reported more painful injections at the botulinum toxin-injected hands.

Discussion

Focal hyperhidrosis is usually confined to the palms, soles and axillae. Excessive sweating may be a social handicap and an occupational hazard. Wet palms give a false impression of uncertainty and nervousness, which often leads to social isolation. A wet grip causes things to slip out of the hands, and it is troublesome in work with paper and metals, an extreme handicap in art work and may be catastrophic for certain professions, such as violin and cello players. This explains why, for severe palmar hyperhidrosis, relatively heroic surgical procedures that lead to sympathetic denervation are considered and performed and why, for severe axillary sweating, a total surgical excision of the axillary skin is the ultimate solution to this socially incapacitating dilemma.[20,21]

The management of focal hyperhidrosis remains controversial. Topical antiperspirants are effective in the mildest cases. Iontophoresis with tap water or anticholinergic drugs is messy and time-consuming with only short-lived effect.[20,21] Biofeedback techniques have been used with limited success.[20] Sympathectomy, the cornerstone of surgical management, is usually effective and longlasting as far as reduced sweating of the palms and axillae is concerned. Complications of this technique include surgical risks, postoperative and cosmetic problems and compensatory hyperhidrosis after several years.[21]

The sweat glands are innervated by ipsilateral postganglionic sympathetic fibres with acetylcholine serving as the transmitter. Botulinum A toxin blocks cholinergic transmission of the sweat glands and therefore reduces sweat production, as shown in earlier experiments.[15–18]

Our double-blind study for the first time shows that botulinum A toxin significantly reduces sweat production in focal hyperhidrosis of the palms over a period of 13 weeks after a single injection. This was demonstrated by objective measurements as well as subjective ratings. Subjective ratings revealed a beneficial effect lasting at least 13 weeks in eight of 11 patients, and two additional patients observed only mild and shortlasting sweat reduction during the observation period. Thus, local injection at multiple sites may be considered a potential form of treatment for palmar hyperhidrosis which could also be expanded to include axillary sweating. Disadvantages of this new treatment are pain during the injection, especially in the palms, and possible local, and reversible, concomitant muscle weakness. Capillary networks at the tips of the fingers impede injections at these sites. Weakness of the small muscles of the hand may be overcome by reducing the total dose of botulinum A toxin and increasing the number of treatment sessions. Several anaesthetic procedures are suitable for reducing pain. We applied ice packs to the palms to minimize pain of injections. The effect was moderate. It will have to be determined whether botulinum A toxin delivery by dermojet is equally effective and less painful.

The long-term effect of local injections of botulinum A toxin on focal hyperhidrosis of the palm also requires further observation. As the therapeutic effect of botulinum A toxin in patients with cranial or cervical dystonias lasts for about 8–12 weeks,[3,6] we chose an observation period of 13 weeks and at the end of our study sweat production was still reduced at the treatment sites. This was true for the objective measurement as well as for the subjective rating. Drobik and Laskawi reported a treatment response lasting for at least 12 months in a patient with Frey's syndrome.[15] Bushara *et al.* observed an anhidrotic effect on test areas on the dorsum of the hands and axillae for at least 6 months.[17] Our self-experiment showed a weakening effect on sweating after 13 weeks,[18] although reduced sweat production was still present after 1 year compared with the non-injected palm.

Owing to the good effect during the observation period, eight of 11 patients included in this study requested continuation of the treatment with botulinum A toxin in an open trial. Long-term follow up is needed to determine whether repeated injections result in sustained benefit without the emergence of tolerance or adverse reactions, especially in terms of weakness of the small hand muscles.

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