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- MacArthur C, Lewis M, Knox EG. *Health after childbirth*. London: HMSO, 1991.
- Wilson PD, Herbison RM, Herbison GP. Obstetric practice and the prevalence of urinary incontinence three months after delivery. *Br J Obstet Gynaecol* 1996;103:154-61.
- MacArthur C, Lewis M, Bick D. Stress incontinence after childbirth. *Br J Midwifery* 1993;1:207-15.
- MacArthur C, Bick DE, Keighley MRB. Faecal incontinence after childbirth. *Br J Obstet Gynaecol* 1997;104:46-50.
- Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI. Anal-sphincter disruption during vaginal delivery. *N Engl J Med* 1993;329:1905-11.
- Berghmans LC, Hendriks HJ, Bo K, Hay-Smith EJ, de Bie RA, van Waalwijk van Doorn ES, et al. Conservative treatment of stress urinary incontinence in women: a systematic review of randomized clinical trials. *Br J Urol* 1998;82:181-91.
- Hay-Smith EJ, Bo K, Berghmans LC, Hendriks HJ, De Bie RA, van Waalwijk van Doorn ES. Pelvic floor muscle training for urinary incontinence in women. *Cochrane Database Syst Rev* 2001;(1):CD001407.
- Sleep J, Grant A. Pelvic floor exercises in postnatal care. *Midwifery* 1987;3:158-64.
- Snooks SJ, Badenoch DF, Tiptaft RC, Swash M. Perineal damage in genuine stress incontinence. An electrophysiological study. *Br J Urol* 1985;57:422-6.
- Wilson PD, Herbison GP. A randomized controlled trial of pelvic floor muscle exercises to treat postnatal urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 1998;9:257-64.
- O'Brien J, Austin M, Sethi P, O'Boyle P. Urinary incontinence: prevalence, need for treatment, and effectiveness of intervention by nurse. *BMJ* 1991;303:1308-12.
- Jozwik M, Jozwik M. The physiological basis of pelvic floor exercises in the treatment of stress urinary incontinence [review]. *Br J Obstet Gynaecol* 1998;105:1046-51.
- Millard RJ. *Bladder control—a simple self-help guide*. Sydney: MacLennan and Petty, 1987.
- Mason L, Glenn S, Walton I, Hughes C. The instruction in pelvic floor exercises provided to women during pregnancy or following delivery. *Midwifery* 2001;17:55-64.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-70.
- Norton C, Hosker G, Brazzelli M. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. *Cochrane Database Syst Rev* 2000;4:CD002111.
- Hosker G, Norton C, Brazzelli M. Electrical stimulation for faecal incontinence in adults. *Cochrane Database Syst Rev* 2000;(4):CD001310. (Accepted 5 July 2001)

Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial

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Abstract

Objectives To evaluate the safety and efficacy of botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis.

Design Multicentre, randomised, parallel group, placebo controlled trial.

Setting 17 dermatology and neurology clinics in Belgium, Germany, Switzerland, and the United Kingdom.

Participants Patients aged 18-75 years with bilateral primary axillary hyperhidrosis sufficient to interfere with daily living. 465 were screened, 320 randomised, and 307 completed the study.

Interventions Patients received either botulinum toxin type A (Botox) 50 U per axilla or placebo by 10-15 intradermal injections evenly distributed within the hyperhidrotic area of each axilla, defined by Minor's iodine starch test.

Main outcome measures Percentage of responders (patients with $\geq 50\%$ reduction from baseline of spontaneous axillary sweat production) at four weeks, patients' global assessment of treatment satisfaction score, and adverse events.

Results At four weeks, 94% (227) of the botulinum toxin type A group had responded compared with 36% (28) of the placebo group. By week 16, response rates were 82% (198) and 21% (16), respectively. The results for all other measures of efficacy were significantly better in the botulinum toxin group than the placebo group. Significantly higher patient satisfaction was reported in the botulinum toxin type

A group than the placebo group (3.3 v 0.8, $P < 0.001$ at 4 weeks). Treatment related adverse events were reported by only 27 patients (11%) in the botulinum toxin group and four (5%) in the placebo group ($P = 0.13$).

Conclusion Botulinum toxin type A is a safe and effective treatment for primary axillary hyperhidrosis and produces high levels of patient satisfaction.

Introduction

Primary hyperhidrosis is a chronic idiopathic disorder of excessive sweating that mainly affects the axillae, the palms, the soles of the feet, and the face. Focal hyperhidrosis causes appreciable social problems in both private and professional life.¹ Profuse sweating can result in skin maceration and secondary microbial infections.² Current treatments for axillary hyperhidrosis are often ineffective, short acting, or not well tolerated.³

Botulinum toxin type A has been used successfully in a range of medical disorders including strabismus, blepharospasm, focal dystonias, and spasticity associated with juvenile cerebral palsy and adult stroke.⁴ In hyperhidrosis, botulinum toxin type A acts by blocking the release of acetylcholine from overactive cholinergic sudomotor nerve fibres. These innervate eccrine sweat glands, so excessive sweating is reduced. Several small, predominantly open label studies and one placebo controlled study have shown that botulinum toxin type A is safe and relieves symptoms of hyperhidrosis for 3 to 14 months.^{2 5-15} We report a 16 week multicentre randomised controlled trial to evaluate the safety and



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efficacy of botulinum toxin type A in bilateral primary axillary hyperhidrosis.

Methods

Recruitment

From March to October 1999, 465 patients from 17 European dermatology and neurology clinics were screened for bilateral primary axillary hyperhidrosis that was sufficient to interfere with daily living. Patients were eligible for the trial if gravimetric tests showed that they produced ≥ 50 mg sweat per axilla over five minutes while at rest at room temperature and were not receiving any other treatment for hyperhidrosis.

Study design and treatment

Participants were randomised to receive treatment in a ratio of 3:1 (botulinum toxin type A to placebo) with a block size of four. The hyperhidrotic area for treatment was defined by Minor's iodine starch test.¹⁶ Participants received a single treatment of 50 U botulinum toxin type A per axilla (Botox, Allergan, Irvine, CA) or placebo (Botox vehicle) as multiple (10-15) intradermal injections evenly distributed within the hyperhidrotic area. Active treatment and placebo were indistinguishable. The trial drug was reconstituted with 4 ml of 0.9% preservative free sterile saline (2 ml for each axilla). Follow up assessments were at 1, 4, 8, 12, and 16 weeks after treatment.

We obtained ethics committee approval for the participating centres, and participants gave written informed consent.

Efficacy measures

The primary efficacy variable was the incidence of responders in each treatment group at week 4. We defined responders as patients with a $\geq 50\%$ reduction from baseline in axillary sweating measured gravimetrically. Secondary efficacy measures included the persistent responders at week 16; the size of the sweat producing area indicated by Minor's iodine starch test; and global assessment of treatment satisfaction score ranging from +4 (complete abolition of signs and symptoms) through 0 (unchanged), to -4 (very substantial worsening).

Safety measures

We recorded the type, incidence, severity, and cause of all spontaneously reported adverse events throughout the trial.

Statistical analyses

We planned to enrol 300 patients (225 treated with botulinum toxin type A and 75 with placebo) to account for an expected dropout rate of less than 10%. This gave a power of 93% to detect a 25 percentage point difference between treatment groups, assuming response rates of 60% and 35% for the botulinum toxin type A and placebo groups respectively, with a two sided significance of 5%. We analysed data on an intention to treat basis. For the primary efficacy measure (incidence of treatment responders), we used the last observation carried forward method to replace missing values and evaluated differences between groups by Fisher's exact test. Within and between group differences of continuous variables, such as sweat production, were assessed by using Wilcoxon signed rank and Wilcoxon rank sum tests, respectively.

Results

Participants

A total of 320 patients with bilateral primary axillary hyperhidrosis were randomised: 242 patients to botulinum toxin type A and 78 patients to placebo. Three hundred and seven completed the trial: 234 (97%) in the botulinum toxin group and 73 (94%) in the placebo group. Of the 13 patients (eight in the botulinum toxin group and five in the placebo group) who withdrew, one withdrew because of an adverse event unrelated to trial treatment, five were lost to follow up, and seven were withdrawn because they did not comply with the protocol.

The mean reported time since the onset of hyperhidrosis was 13.1 (SD 10.4) years in the botulinum toxin group and 13.6 (10.0) years in the placebo group. Other baseline variables, such as other areas of hyperhidrosis and triggers of hyperhidrosis were also similar between treatment groups.

Efficacy

Botulinum toxin type A effectively reduced sweating at all time points after treatment compared with placebo (table). The proportion of responders in the botulinum toxin type A treated group was significantly higher than that in the placebo group at all time points (95% (230) *v* 32% (25) at week 1, 94% (227) *v* 36% (28) at week 4, and 82% (198) *v* 21% (16) at week 16, $P < 0.001$). In addition, the difference in responder rate between the treatment groups at all time points was much greater than the 25 percentage points that we had predefined as being clinically important (63% at week 1, 95% confidence interval 52% to 74%; 58% at week 4, 47% to 69%; and 61% at week 16, 51% to 72%). A significantly higher percentage of patients in the botulinum toxin type A treated group were persistent treatment responders at the end of the study (77%; 182/235) compared with the placebo group (17%; 13/74) ($P < 0.001$). The results for all other measures of efficacy were also significantly better in the botulinum toxin group than the placebo group at all follow up visits (table).

Safety

Most adverse events in both treatment groups were mild or moderate. Twenty seven (11%) patients in the botulinum toxin group reported treatment related adverse events compared with four (5%) in the placebo group; this difference was not significant. Eleven (5%) patients in the botulinum toxin group perceived an increase in non-axillary sweating after treatment compared with none of the control group. All eleven were responders, and increases were reported at various body sites. No clinically important changes in vital signs or findings on physical examination were observed.

Discussion

Primary findings

Our results show a highly significant reduction in the amount of sweating in patients with primary axillary hyperhidrosis after intradermal injections of 50 U botulinum toxin type A. The results are based on the Botox formulation of botulinum toxin type A and cannot be generalised to other formulations or to other serotypes.

The onset of action was rapid and the effect was sustained for at least 16 weeks. Reduction in sweating was accompanied by a high level of treatment satisfaction. Botulinum toxin type A was both safe and well tolerated, with few adverse events reported. These results agree with the preliminary findings of open label studies and one recent double blind study.⁵

Strengths and weaknesses of study

This is one of the first double blind, placebo controlled studies of botulinum toxin type A in axillary hyperhidrosis. The follow up period was limited, but longer term follow up is in progress. Other studies have shown that the treatment remains effective for up to 14 months for various doses.^{5 6 9 17}

Another limitation of the study is that it evaluated only a single treatment. Previous studies of botulinum toxin type A in the treatment of axillary hyperhidrosis have evaluated doses ranging from 30 U to 100 U in each axilla.^{6 9 11 12} Clearly, the optimal dose of botulinum toxin type A is one that effectively reduces sweating to physiologically normal levels for as long as possible while minimising side effects. Although 50 U botulinum toxin type A per axilla was safe and effective in this trial population, some patients may need the dose adjusted to achieve optimal clinical results.

Only one other study of axillary sweating has used a similar controlled design.⁵ However, that study had no pure control group as one axilla was treated with botulinum toxin type A and the other with placebo. Since a different botulinum toxin type A formulation was used, we cannot compare effectiveness and dose with those in our study. Both studies show that botulinum toxin type A is an effective treatment for axillary hyperhidrosis.

Implications

A highly effective treatment with few side effects has the potential to change current treatment strategies for this distressing disorder. Topical and systemic anticholinergic treatments for axillary hyperhidrosis are often ineffective, short acting, or poorly tolerated.³ Surgical

What is already known on this topic

Primary hyperhidrosis is a chronic disorder that can affect any part of the body, especially the axillas, palms, feet, and face

Current treatments are often ineffective, short acting, or poorly tolerated

What this study adds

Botulinum toxin type A was significantly better than placebo on all measures of sweating

Patient satisfaction was high and few adverse events were reported

Effects of treatment remained apparent at 16 weeks

intervention, such as endoscopic transthoracic sympathectomy, is effective but carries appreciable risks, including Horner's syndrome, gustatory sweating, neuralgia, and pneumothorax.¹⁸⁻²⁰ In addition, up to 100% of patients having endoscopic transthoracic sympathectomy develop compensatory hyperhidrosis,¹⁹⁻²¹ resulting in dissatisfaction with the procedure in up to a third of patients.²² Another surgical treatment, excision and curettage of sweat glands in the axillas, can cause scar formation.³

A perceived increase in non-axillary sweating was reported by 11 patients (5%) in the botulinum toxin group of our study. However, these patients did not show reduced satisfaction with treatment on the global assessment of treatment satisfaction scale. This additional sweating was not quantified. Subjective reports of increased non-axillary sweating could have been the result of heightened awareness of sweat production at other sites after the axillas had been successfully treated. Alternatively, the increased non-axillary sweating could reflect a central up-regulation of the autonomic nervous system or may represent minimal compensatory sweating. Reported rates of non-axillary sweating after botulinum toxin type A were much lower than those reported after surgical treatment.¹⁹⁻²¹

In conclusion, botulinum toxin type A is an effective, safe, and well tolerated treatment for patients with primary axillary hyperhidrosis. The treatment is easily administered, patients are easily identified, and repeat treatment has been shown to be effective.¹⁰ Botulinum toxin type A is a valuable alternative to previous treatment options for this disorder.

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Effect of botulinum toxin type A and placebo on sweat production and patient satisfaction

| No of weeks after treatment | Botulinum toxin type A | | Placebo | |
|----------------------------------------------|------------------------|---------------|--------------------|---------------|
| | No of participants | Mean (SD) | No of participants | Mean (SD) |
| Sweat production (% change from baseline): | | | | |
| 1 | 242 | -83.0* (24.1) | 78 | -21.8 (58.7) |
| 4 | 242 | -83.5* (21.6) | 78 | -20.8 (54.4) |
| 16 | 242 | -69.3* (39.4) | 78 | -3.8 (93.5) |
| Absolute sweat production (mg): | | | | |
| 0 | 242 | 215.8 (178.7) | 78 | 235.7 (213.8) |
| 1 | 242 | 28.6* (37.5) | 78 | 166.2 (178.8) |
| 4 | 242 | 28.1* (40.5) | 78 | 153.0 (143.3) |
| 16 | 242 | 53.7* (67.7) | 78 | 190.5 (195.6) |
| Area of sweat production (cm ²): | | | | |
| 0 | 216 | 5.3 (7) | 66 | 6.0 (7) |
| 1 | 224 | 0.1 (1.1)* | 70 | 4.1 (9.2) |
| 4 | 219 | 0.2 (0.7)* | 65 | 4.5 (7.8) |
| 16 | 218 | 0.2 (0.9)* | 71 | 2.3 (5.5) |
| Satisfaction score: | | | | |
| 1 | 67 | 3.1* (1.1) | 24 | 0.8 (1.4) |
| 4 | 85 | 3.3* (0.9) | 29 | 0.8 (1.4) |
| 16 | 204 | 2.6* (1.6) | 61 | 0.3 (1.2) |

*P<0.001 compared with placebo.

- 1 Naver H, Aquilonius S-M. The treatment of focal hyperhidrosis with botulinum toxin. *Eur J Neurol* 1997;4(suppl 2):S75-9.
- 2 Naumann M, Hamm H, Kinkelin I, Reiners K. Botulinum toxin type A in the treatment of focal, axillary and palmar hyperhidrosis and other hyperhidrotic conditions. *Eur J Neurol* 1999;6(suppl.4):S111-5.
- 3 Stolman LP. Treatment of hyperhidrosis. *Dermatol Clin* 1998;16:863-9.
- 4 Hallett M. One man's poison: clinical applications of botulinum toxin. *N Engl J Med* 1999;341:118-20.
- 5 Heckman M, Ceballos-Baumann AO, Plewig G. Botulinum toxin type A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001;344:488-93.
- 6 Glogau RG. Botulinum A neurotoxin for axillary hyperhidrosis. *Dermatol Surg* 1998;24:817-9.

- 7 Heckmann M, Breit S, Ceballos-Baumann A, Schaller M, Plewig G. Side-controlled intradermal injection of botulinum toxin type A in recalcitrant axillary hyperhidrosis. *J Am Acad Dermatol* 1999;41:987-90.
- 8 Naumann M, Flachenecker P, Bröcker E-B, Toyka KV, Reiners K. Botulinum toxin for palmar hyperhidrosis. *Lancet* 1997;349:252.
- 9 Naumann M, Hofmann U, Bergmann I, Hamm H, Toyka KV, Reiners K. Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin. *Arch Dermatol* 1998;134:301-4.
- 10 Naver H, Swartling C, Aquilonius S-M. Treatment of focal hyperhidrosis with botulinum toxin type A. Brief overview of methodology and 2 years' experience. *Eur J Neurol* 1999;6(suppl 4):S117-20.
- 11 Odderson IR. Hyperhidrosis treated by botulinum A exotoxin. *Dermatol Surg* 1998;24:1237-41.
- 12 Odderson IR. Axillary hyperhidrosis: treatment with botulinum toxin type A. *Arch Phys Med Rehabil* 1998;79:350-2.
- 13 Schnider P, Binder M, Berger T, Auff E. Botulinum A toxin injection in focal hyperhidrosis. *Br J Dermatol* 1996;134:1160-1.
- 14 Schnider P, Binder M, Kütler H, Birner P, Starkel D, Wolff K, et al. A randomized, double-blind, placebo-controlled study trial of botulinum toxin type A for severe hyperhidrosis. *Br J Dermatol* 1999;140:677-80.
- 15 Shelley WB, Talanin TY, Shelley ED. Botulinum toxin therapy for palmar hyperhidrosis. *J Am Acad Dermatol* 1998;38:227-9.
- 16 Minor V. Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung. *Dtsch Z Nervenheilkd* 1927;101:301-6.
- 17 Bushara KO, Park DM, Jones JC, Schutta HS. Botulinum toxin—a possible new treatment for axillary hyperhidrosis. *Clin Exp Dermatol* 1996;21:276-8.
- 18 Drott C, Gothberg G, Claes G. Endoscopic transthoracic sympathectomy: an efficient and safe method for the treatment of hyperhidrosis. *J Am Acad Dermatol* 1995;33:78-81.
- 19 Drott C, Claes G. Hyperhidrosis treated by thoracic sympathectomy. *Cardiovasc Surg* 1996;4:790-1.
- 20 Lai YT, Yang LH, Chio CC, Chen HH. Complications in patients with palmar hyperhidrosis treated with transthoracic endoscopic sympathectomy. *Neurosurgery* 1997;41:110-3.
- 21 Kao MC, Chan YL, Lin YJ, Hsieh CA, Tsai JC. Endoscopic sympathectomy treatment of craniofacial hyperhidrosis. *Arch Surg* 1996;131:1091-4.
- 22 Herbst F, Plas EG, Fugger R, Fritsch A. Endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limbs: a critical analysis and long-term results of 480 operations. *Ann Surg* 1994;220:86-90. (Accepted 5 July 2001)

Social factors associated with child mental health problems in Brazil: cross sectional survey

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The prevalence of child psychiatric disorder in the developed world is 10-20%, but in the developing world, where children and adolescents make up a higher proportion of the population, the prevalence may be higher.¹ Relatively little is known about the extent to which social risk factors identified in the developed world also apply in the developing world.¹ To guide healthcare planning we used three contrasting samples from the largest and most populous country in Latin America to examine the association between child mental health problems and social factors, such as poverty, family violence, and parental mental illness.

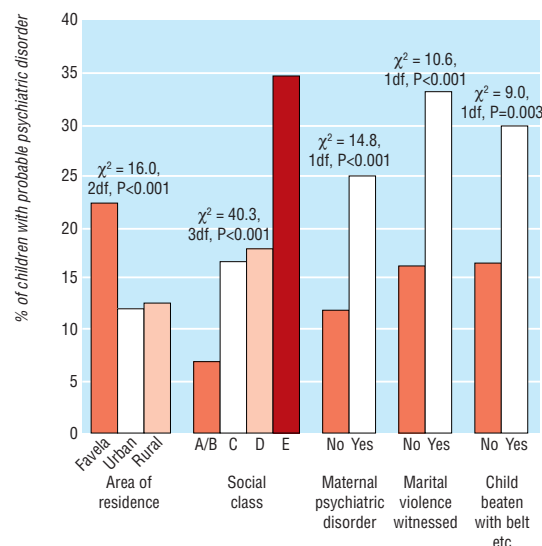
Participants, methods, and results

Three contrasting neighbourhoods were selected from a single district in south east Brazil: a new favela (shanty town) of crowded makeshift dwellings, lacking sanitation, and built on illegally occupied land; a stable urban community; and a rural village. We aimed to identify all 7-14 year olds (compulsory school years) in these three areas from school registers. For the children on school lists, we obtained informed parental agreement to participation for 75% of the children from the favela, 67% from the stable urban community, and 95% from the rural village. Supplementary house to house searches in the favela identified relatively few additional 7-14 year olds who were not on any school list—amounting to only 16% of the favela sample and not differing significantly in social or psychiatric characteristics. The total sample of 898 participating children comprised 488 from the favela, 346 from the stable urban area, and 64 from the rural area.

Children with probable psychiatric disorder were identified by parents, teachers, and self report versions of the strengths and difficulties questionnaire, using a predictive algorithm that has been validated in both developed and developing countries.^{2,3} In this study an independent psychiatric assessment⁴ of randomly chosen children identified a psychiatric disorder in 23 of

41 of those whose questionnaire results suggested psychiatric disorder, compared with six of 40 of those whose results did not ($\chi^2 = 13.1$, 1 df, $P < 0.001$). We assessed social class from affluence and parental education using standard Brazilian criteria—ranging from A/B (middle class) to E (abject poverty and illiteracy). Maternal psychiatric disorder was predicted with the validated Brazilian cut off point on a self report questionnaire (the SRQ-20).⁵ Parents were asked how the child was disciplined and whether the child had witnessed marital violence.

The figure shows the univariate results and their significance. In forward conditional logistic regression, area (whether it was a favela or not) was no longer significant ($P = 0.84$) once the effects of social class, maternal depression, domestic violence, and harsh discipline had been allowed for.



Rates of probable child psychiatric disorder according to social factors

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