Clin Auton Res (2015) 25:201–205
DOI 10.1007/s10286-015-0288-8

RESEARCH ARTICLE

Prediction of compensatory hyperhidrosis with botulinum toxin A and local anesthetic

Jin Yong Jeong[1] · Soo Seog Park[2] · Sung Bo Sim[3] · Keon Hyon Jo[4] · Jongho Lee[5] · Saecheol Oh[6] · Jae Seong Shin[7]

Received: 26 June 2014 / Accepted: 9 February 2015 / Published online: 8 May 2015

Abstract

Objective Compensatory hyperhidrosis (CH) is one of the most problematic complications of sympathectomy, which occurs often and is hard to treat. A predictive procedure (PP) for CH can help patients experience compensatory sweating before sympathectomy to determine whether or not to perform sympathectomy. Our study aimed to evaluate the CH after the PP and sympathectomy in patients with primary palmar hyperhidrosis using multiple drugs.

Methods We reviewed 83 patients who underwent a PP between July 2009 and August 2013 with primary palmar hyperhidrosis. In group A, we used levobupivacaine ($n = 39$). In group B, we used botulinum toxin A plus ropivacaine for the PP in group B ($n = 44$).

Results The CH rate after the PP was 44 % (group A) and 25 % (group B), and after sympathectomy 80 % (group A) and 75 % (group B). The prediction value between the PP and the sympathectomy was statistically significant in

✉ Jongho Lee
phenix@catholic.ac.kr

1 Department of Thoracic and Cardiovascular Surgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Republic of Korea

2 Department of Anesthesiology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Republic of Korea

3 Department of Thoracic and Cardiovascular Surgery, St. Paul's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Republic of Korea

4 Department of Thoracic and Cardiovascular Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Republic of Korea

5 Department of Thoracic and Cardiovascular surgery, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Republic of Korea

6 Department of Anesthesiology, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Republic of Korea

7 Department of Thoracic and Cardiovascular Surgery, Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea

group A ($p < 0.05$). The positive prediction rate was 73 % and the negative prediction rate was 27 % in group A.
Conclusions Local anesthetic alone has a better predictive value. From our finding, patients should be made aware that CH after sympathectomy is less severe in 73 % of cases than that experienced in the PP.

Keywords Compensatory hyperhidrosis · Sympathectomy · Hyperhidrosis

Introduction

Thoracoscopic sympathectomy has become the treatment of choice for primary hyperhidrosis due to the advantages of minimally invasive approaches [1]. However, one of the most problematic complications of sympathectomy is compensatory hyperhidrosis (CH), which occurs afterwards and is often difficult to treat. The predictive procedure (PP) for CH allows patients to experience compensatory sweating before sympathectomy and to establish whether sympathectomy is the appropriate course of treatment [2, 3]. It has been stated previously, however, that the effective duration of local anesthetics used in the PP is too short to evaluate CH after sympathectomy [2].

Botulinum neurotoxins are a family of neurotoxins produced by the anaerobic bacterium *Clostridium botulinum*. As the innervations at both neuromuscular junctions and eccrine sweat glands involve acetylcholine as a neurotransmitter, botulinum neurotoxins, which can block the release of acetylcholine, have been used in the treatment of focal hyperhidrosis. Recently, chemodenervation using botulinum toxin A (BTA) has emerged as a safe and effective treatment for both primary palmar (Level B evidence) and axillary (Level A evidence) hyperhidrosis [4]. The effects of BTA lasted several months to a year [5, 6]. BTA prevents the release of acetylcholine from cholinergic nerve terminals; preganglionic sympathetic nerves are cholinergic, and Kim and colleagues [7] reported that BTA can induce prolonged sympathetic blockade of the superior cervical ganglia in rabbits.

Our study aimed to evaluate CH after PP using local anesthetic alone or local anesthetic plus BTA compared to CH after sympathectomy in patients with primary palmar hyperhidrosis.

Patients and methods

We reviewed 83 patients who underwent a PP between July 2009 and August 2013 with severe primary palmar hyperhidrosis, defined as grade 3 or 4 on the Hyperhidrosis Disease Severity Scale as evaluated by the same surgeon. In group A, we used 5 ml of 0.25 % levobupivacaine HCl (Chirocaine, Abbott S.p.A., Campoverde Di Aprilia, Italy) ($n = 39$) and BTA 40 U (Botox, Allergan, County Mayo, Ireland) plus 5 ml of 0.75 % ropivacaine (Naropin, AstraZeneca UK Ltd., Luton, UK) for the PP in group B ($n = 44$). This study was approved by the Institutional Review Board of Incheon St. Mary's Hospital, College of Medicine, the Catholic University of Korea, and written informed consent was obtained from all patients prior to the PP for CH.

All PPs were carried out under local anesthesia, except in two patients of group A who requested general anesthesia. The patients returned to the hospital 1 week after the PP for an interview. We asked patients about the sites of CH, severity of CH, effective duration of the PP, and relief of primary palmar hyperhidrosis. CH was graded as follows: none, mild, moderate or severe. The final decision regarding sympathectomy for primary palmar hyperhidrosis was made based on the extent and degree of CH and the wishes of the patient.

The results of each group were compared after the PP and sympathectomy. To compare CH between the PP and sympathectomy, we divided patients into *N* (no change between the two procedures), *I* (less severe CH after sympathectomy) and *D* (more severe CH after sympathectomy) groups. We also evaluated the prediction rate by defining positive prediction as cases where CH remained the same or improved between the PP and sympathectomy, while negative prediction was defined as the cases where CH worsened after the sympathectomy compared to the PP.

Surgical technique

The protocol of the PP has been described in a previous report [2]. Briefly, patients were placed in the prone position with temperature probes applied to both palms. Under local anesthesia with 0.5 % lidocaine, a thoracoscopic port with a 2-mm scope (MiniPort 2 mm, Tyco Healthcare UK Ltd., Gosport, UK) was inserted and CO_2 was insufflated into the pleural space to collapse the lung.

A 2-mm thoracoscope was used for visualization as a spinal needle (21 or 23 G × 89 mm, Hakko Co. Ltd., Chikuma, Japan) was introduced through the third intercostal space on the paravertebral line from the patient's back. Then 5 ml of local anesthetic with or without 40 units of BTA was injected extrapleurally around the T3 sympathetic chain and ganglion. After the air in the pleural space was evacuated, the procedure was complete.

Table 1 Patient characteristics of two groups

Variable (n = 83)	Group A (n = 39)	Group B (n = 44)	p value
Sex			>0.05
Male	24	21	
Female	15	23	
Age (years ± SD)	21.1 ± 7.7	25.4 ± 10.7	>0.05
Simultaneous hyperhidrosis (n)			>0.05
Axillary	13	19	
Plantar	32	37	
Face	2	4	
Temperature change (°C ± SD) of PP and sympathectomy	4.1 ± 2.4 2.0 ± 3.0	3.6 ± 2.2 3.8 ± 3.8	>0.05
Effective duration of the PP (Hours ± SD)	30.7 ± 41.1	48 ± 67.8	>0.05
Operation	30 (77 %)	28 (67 %)	>0.05
CH			
PP	17 (44 %)	11 (25 %)	0.06
Sympathectomy	24 (80 %)	21 (75 %)	0.64

Statistical analysis

Data analysis was performed with SPSS (SPSS version 12.0; SPSS, Chicago, IL, USA). Comparisons between groups were assessed with a χ^2 or Fisher's exact test for categorical variables and an unpaired t test for continuous variables. Continuous variables are expressed as mean ± standard deviation. The correlation between two continuous variables was calculated with simple linear regression analysis. A value of $p < 0.05$ was considered to be statistically significant.

Table 2 CH after sympathectomy compared with the PP

Variable	N group	I group	D group	Total
Group A	15	7	8	30
Group B	10	2	16	28
Total	25	9	24	58

Chi-square test (p value) = 0.041109

Results

Baseline characteristics and outcomes

Baseline demographic and clinical parameters are detailed in Table 1. In summary, 38 women and 45 men with a mean age of 23.38 years (range, 12–64 years) underwent the PP. The other sites of hyperhidrosis were plantar in 32 patients, axillary in 13 patients, and facial in 2 patients in group A, and plantar in 37 patients, axillary in 19 patients, and facial in 4 patients in group B. There were no significant differences in sex, age or preoperative hyperhidrosis area between the two groups. Also, there were no statistically significant differences in change of palmar temperature during the PP [29.6 ± 3.0 °C to 33.7 ± 2.9 °C (group A) and 31.9 ± 2.5 °C to 35.5 ± 1.2 °C (group B); $p > 0.05$] or the effective duration of the PP [30.7 ± 41.1 h (group A) and 48 ± 67.8 h (group B); $p > 0.05$]. The CH rates after the PP were 44 % (group A) and 25 % (group B) ($p = 0.06$), and after sympathectomy they were 80 % (group A) and 75 % (group B) ($p = 0.64$).

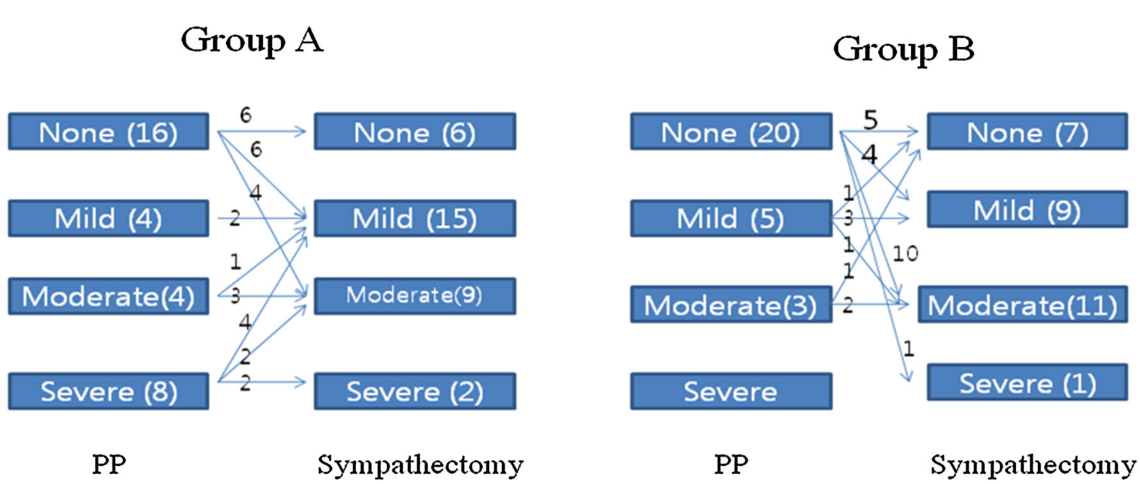

Fig. 1 Differences in the degree of CH between the PP and sympathectomy

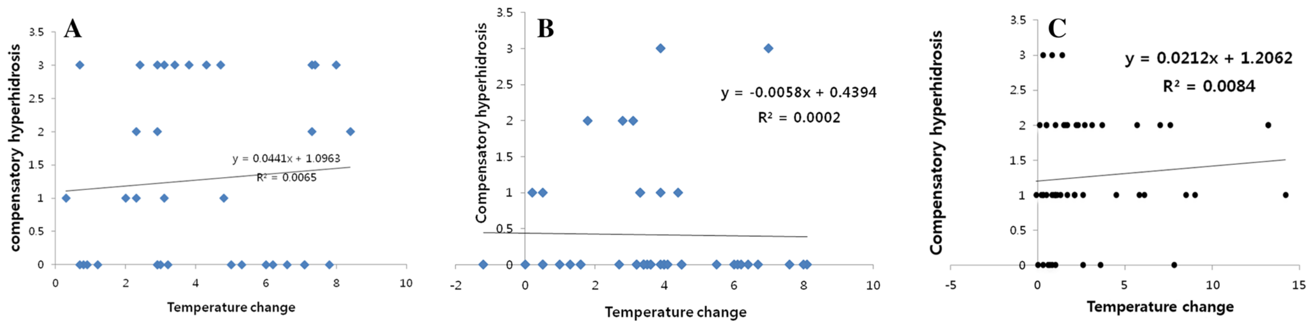

Fig. 2 Relationship between palmar temperature change during the PP and sympathectomy, and CH after sympathectomy (**a** group A, **b** group B; during the PP, **c** during sympathectomy)

CH prediction rate of the two groups

The difference in the degree of CH is summarized in Fig. 1, and the prediction value of the two groups between the PP and sympathectomy was statistically significant in group A ($p < 0.05$). The positive prediction rate was 73 %, and the negative prediction rate was 27 % in group A, while the positive prediction rate was 43 %, and the negative prediction rate 57 % in group B (Table 2).

Correlation between the palmar temperature change during the PP and then during sympathectomy, and CH after sympathectomy

Palmar temperature changes during the PP and sympathectomy were 4.1 ± 2.4 °C and 2.0 ± 3.0 °C in group A and 3.6 ± 2.2 °C and 3.8 ± 3.8 °C in group B, and both $p > 0.05$ (Table 1). There was no statistically significant correlation between the palmar temperature change during the PP and sympathectomy and degree of CH after sympathectomy (Fig. 2).

Discussion

The most serious complication after a sympathectomy for primary hyperhidrosis is CH. The incidence of post-sympathectomy CH is 55–87 %, and the condition is severe in 1–42 % of patients. Our study demonstrated a similar occurrence rate. Severe CH is the most intractable problem of this procedure and a major cause of patient dissatisfaction after sympathectomy [8–11]. Postoperative CH is a major hurdle in sympathectomy for three key reasons: (a) the difficulty of predicting CH occurrence and severity preoperatively, (b) the limited treatment strategy for CH, (c) the difficulty faced by of patients in achieving their preoperative condition or even managing CH symptoms.

There are several methods of treating CH. Stefaniak and colleagues [12] used removal of the clips from the sympathetic trunk, a T6–9 block and regional abdomino-lumbar iontophoresis. The removal of the clips did not resolve compensatory sweating after 1 year of observation. The T6–9 block also did not remedy CH. Regional abdomino-lumbar iontophoresis seems very promising, but further research and follow-up are necessary to establish its efficacy. Some authors have used robotic surgery to reduce CH after sympathectomy. Coveliers and colleagues [13] reported that robotic thoracoscopic selective sympathectomy yields excellent relief of hyperhidrosis and low rates (7.2 %) of compensatory sweating and complication. Robotic surgical systems have the advantage of magnified high-definition three-dimensional visualization and increased instrument maneuverability in a confined space, making it possible to perform selective postganglionic sympathectomy (ramicotomy). However, these robotic systems are expensive and thus accessibility is limited in many countries.

The most effective way to manage CH is to predict it preoperatively and use this information as a determinant of treatment selection. Several articles have reported that, before sympathectomy, patients experienced the CH symptoms that would develop after permanent sympathectomy [2, 3]. However, the duration of local anesthetic effects in the PP is sometimes too short to accurately predict postoperative CH. An alternative method is to insert an epidural catheter around the sympathetic ganglia and to keep injecting local anesthetic for 1 week. However, this technique is very uncomfortable and is associated with an increased risk of infection. Recently, chemodenervation using BTA has emerged as a safe and effective treatment for both primary palmar (Level B evidence) and axillary (Level A evidence) hyperhidrosis [4]. The effective duration of BTA was several months to a year [5, 6]. BTA prevents the release of acetylcholine from cholinergic nerve terminals and therefore induces prolonged sympathetic block. Our study was based on the assumption that

BTA can block sympathetic ganglia long enough to evaluate CH after the PP and would yield a higher prediction rate for CH after sympathectomy compared to the local anesthetic alone.

The difference in the effective duration of the PP was not statistically significant between the two groups, meaning that BTA did not prolong the duration of the PP as expected. The effects of BTA included some sweating, as seen in Fig. 1. The group B patients who chose to proceed with sympathectomy did not exhibit severe CH after the PP. In group A, 8 of 30 patients developed severe CH after the PP. From a clinical point of view, the positive prediction rate was 73 % in group A and 43 % in group B, while the negative prediction rate was 27 % in group A and 57 % in group B. Between the two groups, group A prediction value for post-sympathectomy CH was statistically significant ($p = 0.041$). The total effect of BTA on the PP was that it masked the amount of sweating, but not time on the palm. BTA also decreased the prediction rate.

Takeo and colleagues [14] reported significant correlations between the range of compensatory sweating and intraoperative increases in palmar temperature and blood flow. Our study did not check blood flow, but did investigate palmar temperature change during the PP and sympathectomy. Even though there were some differences, as Fig. 2 demonstrates, there was no statistically significant correlation between temperature change during PP and sympathectomy and CH after sympathectomy. We assumed that these results did not differ based on whether or not sympathetic ganglion block was transient or permanent.

Conclusions

Local anesthetic alone has better predictive value than the combination of local anesthetic and BTA. This may be due to BTA's prevention of release of acetylcholine in preganglionic sympathetic nerves, which could mask CH after PP. Patients should be made aware of our findings, which suggest that when local anesthetic alone is used, CH after sympathectomy is less severe than that experienced in the PP in 73 % of cases, while in 27 % of cases it is worse than predicted.

Acknowledgments On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Tetteh HA, Groth SS, Kast T, Whitson BA et al (2009) Primary palmoplantar hyperhidrosis and thoracoscopic sympathectomy: a new objective assessment method. Ann Thorac Surg 87(1):267–275
2. Jeong JY, Park HJ, Park JK, Jo KH et al (2014) Predictive procedure for compensatory hyperhidrosis before sympathectomy: preliminary findings. Thorac cardiovasc Surg 62(5):434–438
3. Miller DL, Force SD (2008) Temporary thoracoscopic sympathetic block for hyperhidrosis. Ann Thorac Surg 85(4):1211–1216
4. Bhidayasiri R, Truong DD (2008) Evidence for effectiveness of botulinum toxin for hyperhidrosis. J Neural Transm 115(4):641–645
5. Lowe NJ, Glaser DA, Eadie N, Daqqett S et al (2007) Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. J Am Acad Dermatol 56(4):604–611
6. Lowe NJ, Yamauchi PS, Lask GP, Patnaik R et al (2002) Efficacy and safety of botulinum toxin type a in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. Dermatol Surg 28(9):822–827
7. Kim HJ, Seo K, Yum KW, Oh YS et al (2002) Effects of botulinum toxin type A on the superior cervical ganglia in rabbits. Auton Neurosci 102:8–12
8. Dumont P, Denoyer A, Robin P (2004) Long-term results of thoracoscopic sympathectomy for hyperhidrosis. Ann Thorac Surg 78(5):1801–1807
9. Rodriguez PM, Freixinet JL, Hussein M, Valencia JM et al (2008) Side effects, complications and outcome of thoracoscopic sympathectomy for palmar and axillary hyperhidrosis in 406 patients. Eur J Cardiothorac Surg 34(3):514–519
10. Gossot D, Toledo L, Fritsch S, Celerier M (1997) Thoracoscopic sympathectomy for upper limb hyperhidrosis: looking for the right operation. Ann Thorac Surg 64(4):975–978
11. Weksler B, Blaine G, Souza ZB, Gavina R (2009) Transection of more than one sympathetic chain ganglion for hyperhidrosis increases the severity of compensatory hyperhidrosis and decreases patient satisfaction. J Surg Res 156(1):110–115
12. Stefaniak T, Cwigon M, Laski D (2012) In the search for the treatment of compensatory sweating. Sci World J 2012:134547
13. Coveliers H, Meyer M, Gharagozloo F, Wisselink W et al (2013) Robotic selective postganglionic thoracic sympathectomy for the treatment of hyperhidrosis. Ann Thorac Surg 95(1):269–274
14. Fujita T, Mano M, Nishi H, Shimizu N (2005) Intraoperative prediction of compensatory sweating for thoracic sympathectomy. Jpn J Thorac Cardiovasc Surg 53:481–485