Compensatory Hyperhidrosis: Results of Pharmacologic Treatment With Oxybutynin

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Background. Hyperhidrosis may affect nearly 3% of the population, and thoracic/lumbar sympathectomy has been highly effective. Compensatory hyperhidrosis is a risk associated with surgical procedures, and its treatment is both complex and not well defined. Treatment of primary hyperhidrosis with oxybutynin has yielded positive results; however, its use in compensatory hyperhidrosis (CH) has not been described.

Methods. Twenty-one patients (11 female patients) received oxybutynin for severe CH at a median of 5 years after sympathectomy. Patients were evaluated to determine quality of life before starting oxybutynin and 6 weeks afterward; they assigned grades to determine improvement after 6 weeks and at their last consult visit for each site at which they complained of symptoms.

Results. Six and 15 patients underwent operation for axillary hyperhidrosis and palmar hyperhidrosis, respectively. Median follow-up time with oxybutynin was 377 days (49–1,831 days). Most common CH sites were the back (n = 8) and abdomen (n = 5). After 6 weeks, the quality of life improved in 71.4% of patients. Five patients stopped treatment: 2 because of unbearable dry mouth, 1 because of absence of pharmacologic response, 1 because of excessive somnolence, and 1 because of probable tachyphylaxis. At the last visit, 71.4% of patients presented with moderate to major improvement at the main sites at which sweating was noted.

Conclusions. More than 70% of patients presented with improved overall quality of life and improvement at the most prominent site of compensatory sweating. Long-term treatment was ineffective in less than 25% of patients, primarily because of the side effects of dry mouth and somnolence. Oxybutynin appears to be effective in treating bothersome CH.

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The incidence of primary hyperhidrosis may be as high as 2.8% in the United States [1]. It may be a localized complaint (excessive sweating only in the palms of the hands or armpits) or a more widespread problem. Studies have demonstrated a negative impact on quality of life (QOL) as a result of excessive sweating [2], with significant improvement in QOL after its resolution [3, 4].

Treatment includes topical therapy (eg, botulinum toxin and iontophoresis), anticholinergic agents (eg, oxybutynin and glycopyrrolate), and surgical approaches (local excision of sweat glands in axillary hyperhidrosis or procedures involving the sympathetic system). Each treatment offers advantages and disadvantages over its alternatives (reversibility, long-term effectiveness, and side effect profile) [5].

For both video-assisted thoracic sympathectomy and lumbar sympathectomy (LS), there is a definite risk of CH, because the incidence of this postoperative complaint may be as high as 90% [6].

CH may be defined as perspiration in higher quantities than necessary for thermoregulation and in areas that did not have abnormal sweating preoperatively [7]. It is the Achilles’ heel of sympathectomy, because up to 11.2% of patients expressed either dissatisfaction or regret about having the procedure as a result of CH occurring [8].

Oxybutynin is an antimuscarinic drug associated with the resolution of hyperhidrosis, as noted in 1988 [9]. Recently, this treatment was reported [10, 11] as an initial alternative treatment for primary hyperhidrosis—for plantar [12], axillary [13], palmar, [14, 15] and facial [16] sweating—and it has been evaluated in a randomized placebo-controlled trial [17]. However, there are no published articles describing its use in the treatment of CH.

We aimed to evaluate the efficacy of oxybutynin in a series of patients (n = 21) who underwent surgical sympathectomy (thoracic, lumbar, or both) and sought our services because of significantly bothersome CH.

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Patients and Methods

This was a nonrandomized uncontrolled study performed in accordance with the ethics committees of both institutions (Registry: 01582112.6.1001.0071). The ethics committees did not require informed consent because this study was retrospective. Data were retrieved through our dedicated prospective institutional protocol, which has been in use at our facilities since 2001, for all patients with either primary hyperhidrosis or CH.

From September 2007 to September 2013, 21 patients were included in our pharmacologic protocol; they were enrolled if they determined that their CH was severe enough to pursue treatment. Inclusion depended only on each patient’s subjective interest in treating CH. No scales were used. None of the patients had used oxybutynin previously. Patient demographics are summarized in Table 1.

The indications for operation were as follows: 6 patients had axillary hyperhidrosis, and 15 patients had palmar hyperhidrosis. Two patients underwent thoracic and lumbar sympathectomy (for primary palmpoplantar hyperhidrosis and primary axillary-plantar hyperhidrosis).

The exclusion criteria were primary failure of surgical intervention (i.e., persistent hyperhidrosis at the level treated) and an existing contraindication to oxybutynin therapy (eg, closed-angle glaucoma or intestinal obstruction).

In 15 patients, the extent of thoracic sympathectomy could not be assessed (they underwent operations at other facilities and no surgical reports were available). Of the 4 patients in whom the extent of sympathectomy was known, 1 patient underwent operation at T3, another underwent surgical intervention at T4, and 2 underwent T3/T4 sympathectomy. The 2 remaining patients underwent video-assisted thoracic sympathectomy + LS (levels unknown).

The median age of patients who underwent surgery was 28.6 years. The mean interval between operation and the beginning of oxybutynin therapy was 5 years. Most patients (81%) underwent operation at other facilities and sought treatment for CH at our institution. The minimum follow-up time was 49 days.

The following protocol (which has reduced anticholinergic side effects and enhanced adherence) was implemented: During the first week of therapy, patients received 2.5 mg of oxybutynin once a day at bedtime. From day 8 to day 21, 2.5 mg twice a day was given. From day 22 onward, 5 mg twice a day was given. If necessary, the total dose was increased to 20 mg/day. Oxybutynin was provided by the hospital pharmacy.

Three assessments were performed for each study participant: The first occurred before drug initiation, the second after 6 weeks of treatment, and the final assessment at least 24 weeks after beginning the protocol (except for patients who stopped treatment earlier because of side effects). Patients assessed the following: (1) impression of amelioration at the site of hyperhidrosis that necessitated operation, (2) QOL using a valid questionnaire for hyperhidrosis [3] that was used by different authors in this field [18, 19] before beginning pharmacologic treatment, (3) clinical improvement in CH after 6 weeks of therapy, (4) QOL after 6 weeks of CH treatment, (5) clinical improvement in CH at the final visit (the final consultation occurring at least 6 months after the beginning of treatment), (6) complaints of pharmacologic side effects both after 6 weeks and at the last visit, and (7) impression of ameliorated CH symptoms present at other sites at the last visit.

Patients completed the clinical improvement questionnaire according to their subjective perception of the improvement in sudoresis (evaluated on a scale ranging from 0–10, in which a grade of 0 = null, grades 1–4 = slight improvement, grades 5–7 = moderate improvement, and grades 8–10 = great improvement).

Impact of pretreatment CH on patients QOL was classified into 5 different categories, calculated as the summed total score obtained with the protocol. Higher levels indicated greater impacts and worse QOL. When the total was greater than 83, QOL was considered very poor; from 68 to 83, QOL was poor; from 52 to 67, QOL was good; from 36 to 51, QOL was very good; and from 20 to 35, QOL was excellent.

Improvement in QOL after treatment was classified as follows: When the score was greater than 83, QOL was considered much worse; from 68 to 83, QOL was slightly worse; from 52 to 67, QOL was the same; from 36 to 51, QOL was slightly better; and from 20 to 35, QOL was much better.

The following factors were studied: negative impact of CH on QOL before oxybutynin treatment, improvement in patient QOL after treatment, evolution of CH at the

Table 1. Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Numeric Data</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>n = 10</td>
<td>47.6</td>
</tr>
<tr>
<td>Female sex</td>
<td>n = 11</td>
<td>52.4</td>
</tr>
<tr>
<td>Age at operation, y (range)</td>
<td>14–54</td>
<td></td>
</tr>
<tr>
<td>Age at operation (mean ± standard deviation)</td>
<td>28.6 ± 10.7</td>
<td></td>
</tr>
<tr>
<td>BMI, median ± standard deviation</td>
<td>24.4 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>BMI, range</td>
<td>19.1–33.5</td>
<td></td>
</tr>
<tr>
<td>Quality of life before pharmacologic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td>n = 5</td>
<td>23.8</td>
</tr>
<tr>
<td>Poor</td>
<td>n = 12</td>
<td>57.1</td>
</tr>
<tr>
<td>Good</td>
<td>n = 3</td>
<td>14.3</td>
</tr>
<tr>
<td>Very good</td>
<td>n = 0</td>
<td>0</td>
</tr>
<tr>
<td>Excellent</td>
<td>n = 1</td>
<td>4.8</td>
</tr>
<tr>
<td>Total</td>
<td>n = 21</td>
<td>100</td>
</tr>
<tr>
<td>Quality of life after 6 weeks of oxybutynin treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much worse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Worse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Same</td>
<td>n = 6</td>
<td>28.6</td>
</tr>
<tr>
<td>Slightly better</td>
<td>n = 8</td>
<td>38.1</td>
</tr>
<tr>
<td>Much better</td>
<td>n = 7</td>
<td>33.3</td>
</tr>
<tr>
<td>Total</td>
<td>n = 21</td>
<td>100</td>
</tr>
</tbody>
</table>

BMI = body mass index (kg/m²).
main site of symptoms (comparing the results after 6 weeks of treatment with the results at the last follow-up visit), improvement at the last consult at the other sites of hyperhidrosis, and complications.

**Statistical Analysis**

Means and standard deviations were used in the descriptive analysis of parametrically distributed continuous variables, whereas frequencies were used for categorical variables. McNemar’s test was used to compare self-reported improvements in hyperhidrosis and dry mouth over time at 2 consecutive analysis time points. For all analyses, \( p = 0.05 \) was considered statistically significant.

**Results**

All patients reported significant improvement at the primary site of hyperhidrosis after operation and considered themselves sweat free in these areas.

Mean follow-up time was 377 days (range, 49–1,831 days). Five patients stopped treatment because of side effects: 2 because of severe dry mouth (1 at 92 days and the other after 126 days). One patient discontinued therapy after 91 days because the medication did not have an effect, and another withdrew from the study after 353 days because of excessive somnolence. A fifth individual stopped treatment after 471 days because the medication stopped working.

The most bothersome sites for CH were the back (\( n = 8 \)) and abdomen (\( n = 5 \)). Three patients reported that their CH was more uncomfortable in the thorax; 3 experienced significant symptoms in the feet, and 2 indicated that the groin was the primary site of CH.

QOL before treatment and 6 weeks after treatment is detailed in Table 1. Seventeen patients presented with either poor or very poor QOL before starting oxybutynin. After 6 weeks, 15 patients reported a somewhat improved QOL.

Improvements in sweating (at the main site of CH) after 6 weeks and at the last visit are presented in Table 2. After 6 weeks, 71.4% of patients reported moderate to major improvement in sweating; the same percentage (71.4% or 15 of 21) reported moderate to major improvement in sweating at the last visit. Additionally, 71.4% of patients experienced moderate to major improvement at their second most troubling CH site.

Comparing the categories of improvement after 6 weeks and at the last evaluation (Table 2), 80.95% of patients remained in the same category of improvement, whereas 14.29% of patients “downgraded” their level of improvement, and 4.76% of patients improved over the course of the study. The change in subcategories was not statistically significant (McNemar’s test, \( p = 0.402 \)).

The following side effects were observed: moderate to severe dry mouth in 11 patients (2 stopped treatment because of this complaint), somnolence in 2 patients (1 ceased treatment), mild constipation (1 patient improved after alimentary reeducation), and gastroesophageal reflux (1 patient).
Consistent, 71.43%; improvement, 9.52%; worsening, 19.05%.

Comparisons of dry mouth complaints after 6 weeks and at the last visit are shown in Table 3: 71.43% of patients remained in the same category (absent to light or moderate to severe) throughout the study period, whereas 9.52% improved and 19.05% reported worsening of this symptom.

**Comment**

Sympathectomies have been performed for many decades in both sexes, with similar results obtained in each [20]. After the advent of video-assisted operations, the number of excessive sweating interventions skyrocketed [21]. Unfortunately, patient selection has not been as strict as it should be, and there are patients who may benefit from other treatments, eg, axillary hyperhidrosis patients should be offered mostly topical treatments such as botulinum toxin or aluminum chloride, or, alternatively, sweat gland resection, and patients should be referred for sympathectomy only when such treatments have failed. This faulty patient selection process has unfortunately contributed to the significant increase in the incidence of CH. Less invasive techniques have been developed for LS, with a significant increase in the volume of cases treated with these procedures [22].

Epidemiologically, CH is a minor/rare side effect; however, for a fraction of patients, it becomes so overwhelming that regret arises after operative procedures. Most patients in our study had poor/very poor QOL at enrollment (1 patient reported excellent QOL before treatment; she underwent operation for axillary hyperhidrosis but also exhibited less severe primary plantar hyperhidrosis. CH at her stomach and back was bothersome enough to pursue treatment, after which her plantar hyperhidrosis also improved). Because all patients presented with great improvement at the sites of primary hyperhidrosis after operation (and maintained this improvement at enrollment; these patients stated that there was no sweating at the primary sites), it is very likely that the poor QOL is attributable to CH. Unfortunately, preliminary data seem to indicate that spontaneous long-term amelioration does not occur [23].

There are limited options for those with CH. Clips (if used) can be removed [24, 25], preferably as soon as possible after operation, to prevent permanent nerve damage; if they were not used, chain reinnervation may be attempted, using either a sural nerve [26] or an intercostal nerve [27] graft. The results are not homogeneous for these approaches.

Another possible method of dealing with CH is the use of topical therapy at the sites of CH [28]. However, topical therapy was most likely used before surgical intervention and did not have a significant effect (otherwise, the patient would not have wanted the operation). Thus, it is unlikely that topical therapy can be used to achieve a significantly improved outcome. There have been case reports describing the risk of clinical botulism use [29] during the treatment of primary focal hyperhidrosis, and this risk is theoretically higher if larger areas are treated.

In these settings, a pharmacologic approach with systemic effects (because CH may occur in more than 1 area simultaneously) seems to be an adequate alternative. As with any other therapy, patient and physician must make a decision about how long pharmacologic therapy will be continued, weighing symptom severity against the risk of adverse effects associated with the drug in question; there have not been any studies with very long-term use of any anticholinergic agent used in the treatment of hyperhidrosis to prove its safety.

Glycopyrrolate (an anticholinergic agent somewhat similar to oxybutynin) has been studied for the treatment of CH [19]: 19 patients were evaluated, and short-term results (1 month) demonstrated a significant improvement in QOL after the use of this anticholinergic drug. During follow-up, none of the patients stopped taking the medication, and its main side effect was dry mouth. Glycopyrrolate was not used in our patients because this drug is not widely available in our country. None of the patients in our cohort had previously used oxybutynin; we can only hypothesize that if they had a poor outcome with oxybutynin therapy before operation, they would not have had a different outcome after operation. Conversely, there are few alternative treatments available, and if patients with an unfavorable response to oxybutynin before operation have the misfortune of CH developing, retreatment with oxybutynin may be considered as a therapeutic test.
We have used the following 2 measurements to evaluate the treatment of hyperhidrosis: the de Campos scale [3], to assess QOL before treatment and 6 weeks after treatment, and a self-reporting scale (from 0–10) to evaluate patients’ impressions of improvement at each site of hyperhidrosis, because this symptom may be ameliorated at 1 site but not in others.

Regarding the QOL assessment, there was a statistically significant improvement in our series of patients (pretreatment = 75.24 versus posttreatment = 43.48; \( p = < 0.001 \)), which is similar to the outcome of the study by Gong and colleagues [19]. Because of the retrospective nature of our study, we were unfortunately only able to assess QOL after 6 weeks of treatment and not at the last consult. When we compared QOL improvement with the improvement noted in the sweating self-assessment at 6 weeks, it seemed as though the improvement in QOL was not as high as that noted in the self-assessment. It is possible that the side effects that arose after therapy diminished the positive impact of reduced sweating.

Regarding the assessment of improved hyperhidrosis, although one could argue that an objective assessment of hyperhidrosis (which is technically feasible [30] with sudorometers) may have been performed, we did not perform such measurements. Sudorometers record only 1 specific point in time rather than recording throughout the day. Because hyperhidrosis is a bothersome but not lethal condition and the goal of treatment is the subjective amelioration of the patient’s symptoms, we believe that self-reporting may be an adequate method of data collection.

 Interruption of treatment occurred in 5 patients in our series, all after 1 month (the first after 49 days and the last after 1 year). A study by Gong and colleagues [19] followed patients for only 30 days, making it impossible to compare the severity of side effects between drugs. The patient who discontinued the drug because its effects ceased did not gain weight or have any other clinical intercurrent condition throughout the period in question, and we believe that tachyphylaxis may have occurred. In our series, half the patients were followed for roughly 1 year (median follow-up, 377 days); longer follow-up is necessary to determine whether tachyphylaxis occurs after more than 1 year has passed.

Regarding symptom amelioration at the last visit, most patients (71.4%) demonstrated either moderate or significant improvement at the main site of CH as well as at the other affected sites. For those who did not exhibit a positive response at the main site, the other sites were also unaffected.

Of the patients who showed a poor response to pharmacologic therapy (n = 3), 2 stopped taking the medication. The other patient maintained treatment because she believed it had an effect on cooler (or less warm) days.

A drawback of this study is the small number of participants (n = 21), which precludes major statistical assumptions. Conversely, to the best of our knowledge, no other series has been published featuring either more patients or a longer follow-up period for individuals receiving pharmacologic treatment for CH. Because it is not practical in our institutions to contact patients for longer follow-up information (eg, make phone contact to find out if tachyphylaxis has developed in other patients), we expect them to return at their appointments every 6 or 12 months, and we plan to describe a longer follow-up series after a median of 3 years of follow-up.

Another shortcoming of this study is the lack of surgical information. Because most of our patients underwent operations outside our institution, we could not assess the level at which sympathectomy was performed, and we could not subsequently correlate this information with the severity of CH or a particular patient’s responsiveness to oxybutynin. Although there is literature to support the notion that CH differs in severity as a result of sympathectomy at different locations [31], treatment is necessary for any patient complaining of symptoms, regardless of which ganglia were surgically treated. The retrospective nature of the study, the relatively small number of participants, and the somewhat short follow-up duration (although this appears to be the longest series studied) allow, at best, a description of a possible role for anti-cholinergic therapy in managing CH. Prospective, randomized, and placebo-controlled studies are necessary for an unequivocal evaluation of the treatments for this clinical entity.

Conclusions
Our preliminary study revealed that patients in whom severe CH developed appeared to respond well to oxybutynin. For the patients who did not have significant side effects, therapy appeared to be long lasting (with only 1 case of possible tachyphylaxis noted). For those who did not respond well to oxybutynin, attempts with either local therapy or nerve restoration may be possible.

References
INVITED COMMENTARY

Teivelis and colleagues [1] illuminate yet again a well-recognized but poorly understood neurophysiologic side effect of sympathetic operations—that of compensatory hyperhidrosis (CH), occurring predominantly on the truncal regions. The treatment of patients with severe, problematic compensatory sweating is difficult and somewhat limited, but can include anticholinergic agents such as oxybutynin or glycopyrrolate. Most of the 21 patients in the Teivelis and colleagues’ report showed improvement in their CH with oxybutynin treatment, but the anticholinergic side effects became very problematic for some.

What needs to be emphasized in no uncertain terms is that the best treatment of CH is prevention by appropriate patient selection and judgment. This appears far more important than the specific ganglion level of the sympathetic intervention per se. Mild hand moisture is not an indication for sympathectomy. The patients happiest with sympathetic operations are those with massive, dripping, debilitating palmar hyperhidrosis, usually exhibiting the classic palmpoplantar hyperhidrosis pattern. It is these patients who complain the least about their CH. The complaints of CH are consistently worse for patients with axillary hyperhidrosis or mild palmar hyperhidrosis than for the appropriate, classic cases of typical palmpoplantar hyperhidrosis.

Is this because of truly quantitatively less compensatory sweating in severe palmar cases, or simply that the resulting CH is so much less disabling than the original palmar hyperhidrosis? The answer is not known. What is known is that it is a rare patient indeed who regrets the cure of his or her massive dripping palmar sweating because of seemingly debilitating truncal CH.

Did the patients with severe CH in Teivelis and colleagues’ study really need the sympathetic intervention in the first place? In 6 of the 21 patients, the original sympathetic intervention was done for axillary hyperhidrosis; perhaps these axillary patients (and perhaps all 21 patients) might not have undergone the operation if a rigid selection criteria had been used.

Topical aluminum chloride and botulinum toxin works better and reversibly for axillary hyperhidrosis than palmar hyperhidrosis. Is this because of truly quantitatively less compensatory sweating or much better for axillary hyperhidrosis than palmar hyperhidrosis, and one or both should be tried before resorting to sympathetic intervention for the axilla. Even local axillary sweat gland resection or liposuction techniques are likely preferable to sympathectomy.