Chemomyectomy of the Orbicularis Oculi Muscles for the Treatment of Localized Hemifacial Spasm

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Abstract:
Objective: To report our experience with doxorubicin chemomyectomy as an alternative to other treatments for hemifacial spasm (HFS).
Design: A prospective, open study Phase I clinical trial of chemomyectomy.
Setting: A hospital-based, referral neuro-ophthalmology and oculoplastic service.
Patients and Methods: Repeated (1-6, median: 4) local injections of doxorubicin were given in the eyelids of 8 patients (5 men, 3 women, average age: 71).
Main Outcome Measures: Eyelid strength, self-reported spasm, and duration of improvement without seeking additional or alternative treatments.
Results: Chemomyectomy resulted in permanent (≥2.5 years) orbicularis oculi weakness and relief from spasms in the treated areas in 5 patients, although 2 patients requested occasional supplementary botulinum toxin (BT) injections in the facial muscles over the cheek. One patient had a successful result for 3 years, after which spasm recurred. One patient maintained a successful result in the eyelid but had a failed microvascular decompression in the lower face. One incompletely treated patient required microvascular decompression following spread of spasms to the lower branches of the facial nerve and increased severity of the HFS. One patient required eyelid surgery because of concurrent spastic entropion. One patient treated with a higher concentration than currently used required closure of a skin ulcer.
Conclusions: Doxorubicin chemomyectomy is an effective alternative to conventional therapy for properly selected patients affected by HFS, particularly older patients with relatively localized eyelid muscle spasms. The modified technique of doxorubicin chemomyectomy has developed to the point where its safety is demonstrated and its risks are known.
Key Words: Hemifacial spasm—Blepharospasm—Doxorubicin—Orbicularis oculi myectomy—Chemomyectomy.

Hemifacial spasm is a chronic condition causing contraction of the eyelids and other muscles innervated by the facial nerve. It can be a cause of significant disability, forcing changes in the patient's work or lifestyle. This paper describes our experience with doxorubicin chemomyectomy and compares three alternative treatments for hemifacial spasm (HFS): surgical microvascular decompression with the goal of permanent relief (1-3), chemodenervation with injections of botulinum A toxin (BT) for temporary relief (4-6), and surgical orbicularis myectomy (7,8). Most cases are due to microvascular compression of the facial nerve at its root exit zone near the brainstem.

In an effort to provide a more permanent form of treatment for orbicularis oculi spasm, doxorubicin chemomyectomy was developed. The procedure takes advantage of the myotoxicity of doxorubicin in skeletal muscles. Doxorubicin chemomyectomy has developed on the basis of a continuing and extensive series of laboratory investigations (9-12). Our clinical experience through May 1990 in patients with benign essential blepharospasm and HFS has been reported (13). In reviewing our experience to March 1994, we have had more success in completion of the protocol with patients whose diagnosis was HFS than in those with benign essential blepharospasm. We believe the data reported here serves as the basis for recommending doxorubicin chemomyectomy as an alternative therapy to selected patients with relatively localized ocular muscle spasms as a part of HFS.
PATIENTS AND METHODS

Chemomyectomy was performed in eight patients (5 men, 3 women, average age: 71 years) with hemifacial spasm with approval from the University of Minnesota Committee on the Use of Human Subjects in Research and a Phase I clinical trial authorized by the United States Food and Drug Administration. Informed consent was obtained from the patients. All patients had had reasonably effective responses to botulinum A toxin, but were desirous of having a response lasting longer than 3 months. We excluded patients who had recent myocardial infarction, cardiomyopathy, cardiac arrhythmia, congestive heart failure, bone marrow depression or other hematologic abnormalities, kidney or liver failure, pregnancy or the substantial possibility of future pregnancy, unexplained alopecias, especially of the eyelids, non-Caucasians in whom treatment could result in pigment loss, persons with unwrinkled eyelid skin in whom scarring would be highly evident, and persons with impaired eyelid function, corneal ulcers, keratitis, or dry eyes. Eyelids with insufficient prior orbicularis myectomies were also excluded. Laboratory studies were obtained at the time of the first injection and repeated at approximately 1-year intervals if injections continued. The studies and required values were as follows: hemoglobin (between 11.0 and 15.5 g/dl), leukocyte count (>3,500/mm$^3$), aspartate aminotransferase (AST) (<33 units).

We reported previously (13) concerning chemomyectomy for all forms of eyelid spasms. This study began in April 1988. The present report was prepared because the results with HPS are presently better defined than those with botulinum toxin as performed by Scott: 0 = none; 1 = mild noticeable fluttering, not incapacitating; 2 = moderate noticeable spasm, mildly incapacitating; 3 = severe incapacitating, unable to read, write, drive, etc. The use of the self-reporting spasm intensity scale was problematic, except when the spasms were almost completely absent in the entire face. The patient was asked to report spasms in the treated eyelids only. The improvement rating is obtained by subtracting the final posttreatment spasm from the initial. We thus developed another scale, “Improved Days,” which is defined as the interval between the most recent examination or interview patient encounter and the patient’s most recent doxorubicin injection, during which time the patient reported improvement of spasm and did not receive subsequent orbicularis myectomy, neurovascular decompression surgery, nor botulinum A toxin injections to the treated area. In order to be counted as “improved,” the patient’s self-reported spasm in the treated area had to have been 2 or greater, and at least 180 days had to have passed since the patient’s most recent doxorubicin injection. All patients in the presently reported series have now been followed at least 18 months since their last injection of doxorubicin and are considered tentative “cures.” Our comments on the indications for surgical myectomy are based on a series of four women (average age: 70 years) with HPS and age-related dystrophic keratopathy of the eyelids treated with unilateral upper and lower eyelid or-
bicircularis myectomy on the side of the HFS, combined bilateral upper eyelid blepharoplasties with correction of eyelid and eyebrow ptosis as needed.

RESULTS

Each doxorubicin injection was followed by 1 to 8 weeks of local swelling and/or bruising of the tissue. Sometimes the black, blue, and yellow discoloration would extend as far down as the angle of the mandible. The injected area was tender to touch but not spontaneously painful until healing occurred. The data for the HFS patients treated with chemomyectomy is summarized in Table 1. All of the patients have been followed for more than 2.5 years since the last doxorubicin injection.

Five of these patients have not had any subsequent treatment and are tentatively regarded as "permanent" cures. One of the patients (No. 13) had a recurrence of chemomyectomy in the lower zygomatic and buccal branches of the facial nerve. This patient required two repairs, as the first excision was reduced from 2.0 to 1.0 mg/ml. Since then patients have noticed transient blisters that cleared before they returned for scheduled appointments. One patient with HFS (No. 18) developed a 1-cm ulcer on his cheek at an injection site when a concentration of doxorubicin of 2.0 mg/ml was used. This patient required two repairs, as the first excision was not sufficiently large, and he reports continuing discomfort in that area. He is, however, satisfied with his result. One chemomyectomy pa-

<p>| TABLE 1. Improvement and sequelae following doxorubicin chemomyectomy for hemifacial spasm |
|---------------------------------|-------------------------------|------------------|------------------------|------------------------|-----------------------------|-----------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Sex</th>
<th>Age</th>
<th>Cum's DXR dose (mg)</th>
<th>Improvement</th>
<th>Total no. DXR inj</th>
<th>Cum's DXR dose, mg (no. of Inj)</th>
<th>Date of last DXR</th>
<th>Improved days*</th>
<th>Subsequent surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>M</td>
<td>71</td>
<td>7.00</td>
<td>3</td>
<td>6</td>
<td>Upper lid: 1.0 (1), Lateral canthus: 0.0 (2), Lower lid: 0.0 (2)</td>
<td>2/16/91</td>
<td>1128</td>
<td>Failed NeuroV Decompl. 10/92 for lower face Ulcer repair 2/91, 11/91</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>81</td>
<td>5.60</td>
<td>4</td>
<td>4</td>
<td>Upper lid: 2.0 (2), Lateral canthus: 0.5 (2), Lower lid: 0.5 (2)</td>
<td>2/12/90</td>
<td>1124</td>
<td>NeuroV Decompl 4/91</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>77</td>
<td>5.50</td>
<td>4</td>
<td>4</td>
<td>Upper lid: 1.4 (2), Lateral canthus: 0.3 (1), Lower lid: 0.3 (1)</td>
<td>7/16/91</td>
<td>975</td>
<td>NeuroV Decompl 2/91, 11/91</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>77</td>
<td>4.60</td>
<td>4</td>
<td>4</td>
<td>Upper lid: 1.2 (1), Lateral canthus: 2.0 (2), Lower lid: 1.4 (1)</td>
<td>2/12/90</td>
<td>1124</td>
<td>NeuroV Decompl 4/91</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>55</td>
<td>4.20</td>
<td>4</td>
<td>4</td>
<td>Upper lid: 1.0 (1), Lateral canthus: 1.0 (1), Lower lid: 2.2 (2)</td>
<td>3/12/90</td>
<td>1471</td>
<td>NeuroV Decompl 4/91</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>73</td>
<td>4.00</td>
<td>3</td>
<td>2</td>
<td>Upper lid: 1.0 (1), Lateral canthus: 0.7 (2), Lower lid: 2.3 (2)</td>
<td>10/1/90</td>
<td>1265</td>
<td>NeuroV Decompl 4/91</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>66</td>
<td>4.00</td>
<td>2</td>
<td>2</td>
<td>Upper lid: 1.0 (1), Lateral canthus: 0.3 (1), Lower lid: 1.2 (1)</td>
<td>12/17/90</td>
<td>0</td>
<td>NeuroV Decompl 4/91</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>78</td>
<td>0.80</td>
<td>0</td>
<td>1</td>
<td>Upper lid: 0.0 (2), Lateral canthus: 0.8 (1), Lower lid: 0.8 (1)</td>
<td>4/17/90</td>
<td>0</td>
<td>NeuroV Decompl 4/91</td>
</tr>
</tbody>
</table>

DXR, doxorubicin; Cum's, cumulative; Pt, patient; Inj, injection; BT, Botulinum A toxin; NeuroV, neurovascular; Decomp, decomposition.

* Improvement rating: initial degree of spasm minus the degree of spasm reported at the last patient encounter.

* Improved days: see text for definition.

Late failure after 3 years.
DISCUSSION

This study indicates that doxorubicin chemomyectomy is a reasonably safe and effective treatment for localized HFS when it most symptomatically involves the orbicularis oculi muscle or for treatment of patients with more generalized HFS who would be satisfied with relief of the ocular component of their symptoms. No patient was discontinued from the study on the basis of systemic toxicity or change in the baseline laboratory tests that were repeated yearly. No evidence of local precancerous skin changes was observed clinically or in the one doxorubicin-treated blepharospasm patient whose eyelids were subsequently biopsied (15). Table 1 summarizes the doses used and helps to establish guidelines for treatment. The important parameters are the cumulative dose required for an adequate response in each lid and the maximum dose that can be delivered at one injection. The duration of treatment is a function of the number of doses required. Relief occurred following 1 to 6 injections (median: 4).

The maximum cumulative dose of doxorubicin required for improvement in a single patient was 7 mg, and the minimum was 4 mg, delivered in two to six injection sessions. The minimum cumulative effective dose for an upper eyelid was 1.0 mg and the maximum cumulative dose used was 2.0 mg, while for the lower eyelid, the minimum cumulative effective dose was 1.3 mg and the maximum cumulative dose used was 2.7 mg. The maximum dose on a single occasion was 1.0 mg for the upper lid and 1.3 mg for the lower lid. The eyelid protractors in the adjacent lateral canthal region were often simultaneously injected with either the upper or lower eyelid. The maximum cumulative dose in the lateral canthal region was 1.2 mg, and a typical low dose was 0.3 mg injected on each of two occasions. The maximum cumulative dose for injection in the cheek was 2.7 mg with the maximum on one occasion of 1.5 mg. The cheek and lower eyelid should not be injected simultaneously to prevent excessive local tissue reaction that could lead to cicatricial ectropion. Cheek doses may cause atrophy of the subcutaneous fat and create an unaesthetic dimple or crater over or below the zygomatic arch.

We do not recommend the use of doxorubicin chemomyectomy for patients who do not meet the inclusion and exclusion criteria stated above. We specifically exclude young patients because the teratogenic and carcinogenic potential of doxorubicin is unknown, although the drug has a relatively short half-life as an intact compound, which per-
be the major deterrent to completion of the re-
pletion of treatment, the treated eyelids are less
injections with fewer interruptions. After the com-
pletion of treatment, the treated eyelids are less
flaccid, pinker (due to loss of subcutaneous tissue),
and younger-looking (presumably due to in-
creased density of the connective tissue or loss of
preseptal and subcutaneous fat) than the opposite
lid (Fig. 1). We have not yet broached the subject
of a balancing “chemical blepharoplasty” of the
opposite eyelids.

To justify the “improved days” outcome mea-
sure, we note that except for microvascular decom-
pression, none of the treatment modalities dis-
cussed can offer the patient the reward of total,
permanent cure if it is successful. All of the other
treatments are a compromise involving the pa-
tient’s evolving perception of the risks, costs, and
benefits of the alternative treatments. Thus we be-
lieve the recording of “improved days” following
chemomyectomy is a valid measure of the patient’s
perception that the treatment has an optimal result
beyond which no other treatment is worth pursu-
ing. The reasons for patients dropping out of a
clinical trial include reasons related to the disease
(disencouragement and/or failure to appreciate any
improvement), the medication (adverse reaction or
unpleasant properties), the clinical trial itself (loss
of interest or onerous requirements) and others
(moving away, discouragement by friends or family,
temporary or recurrent illness) (16). All of these factors
were identified as operative during our clinical
trial. However the choice by patients to return and
not have botulinum A toxin treatment in the chemomyectomy-treated areas should be taken at
face value, especially when the two patients chose
to have botulinum A toxin injected in adjacent
chec areas. These patients are not dropsouts from the study and serve to validate the
“improved days” methodology. We would accept
as a valid criticism that we did not use a “masked
questionnaire” or a disinterested party to perform
the interview, although intake interviews on the
return visit are performed by a nurse who is not
rewarded for reporting successful results. In re-
gard to those blepharospasm patients who have
dropped out because of pressure from friends or
family, the main reason was the bruised appear-
ance of the face and the suggestion that this was
the result of an attack by the patient’s husband.
This became such a recurrent theme that we have
designed a large button for the patient to wear
with a cartoon and caption “The Doctor Did It!”

While no patient in the hemifacial spasm chemomyectomy series required an ectropion repair for
an injection complication, one patient in our trial
blepharospasm series did require such a repair.
These surgical repairs are relatively minor but do
add to the cost and must be considered in advising
the patient concerning risks and benefits. One pa-
tient (No. 17) had pain associated with an ulcer at
the injection site over the zygomatic arch.

Table 2 compares and contrasts four alternative
treatments for HFS. The comparisons are general
and application to each patient must be individu-
alized. Both chemomyectomy and surgical myec-
tomy could be considered for patients over 50
years of age. We have not yet performed doxoru-
ubicin chemomyectomy in patients younger than
50, but there is no absolute contraindication. Sur-
gical myectomy resolves concurrent problems as-
associated with the aging eyelid, particularly ptosis,
which can be repaired simultaneously. Con-
versely, ptosis may be recurrently exacerbated by
botulinum A toxin injection in some patients even
when the dose is reduced and the injection given
at the eyelash base in order to be as far away as
possible from the levator palpebrae superioris
muscle. The complete paralysis induced by botuli-
num toxin injection in the lower eyelids of young
patients is welcome but the lack of any muscle tone
can cause severe symptomatic paralytic ectropion
in the aged eyelid. In this circumstance the lesser
degree of paralytic ectropion produced by chem-
omyectomy and surgical myectomy can be helpful.
Both of the myectomies may lead to cicatricial ec-
tropion that may require correction. None of the
three other treatments preclude subsequent use of
botulinum toxin. The myectomies allow the botu-
linum toxin to have increased effect due to de-
creased baseline muscle strength in the myecto-
mized eyelid.

The cumulative cost estimates (Table 2) consid-
ered factors including the economic value of the
time expended by the patient as well as health care
professional, cost of drugs, operating room, hos-
pital charges, and the cost of any secondary sur-
geries that may be required. Table 2 may be helpful
in explaining the alternative therapies to the pa-
tient. In estimating that the cumulative cost asso-
ciated with botulinum toxin therapy is the highest
(4+) on the scale, we have allowed for only one
TABLE 2. Comparison of alternative treatments for hemifacial spasm

<table>
<thead>
<tr>
<th>Branches of facial nerve treated</th>
<th>Patient age</th>
<th>Indications</th>
<th>Potential complications/exacerbated problems</th>
<th>Result duration</th>
<th>Secondary surgery (if required)</th>
<th>Subsequent BT treatment</th>
<th>Cumulative cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvascular decompression</td>
<td>All</td>
<td>All</td>
<td>Orbicularis weakness induced</td>
<td>Complete</td>
<td>Repeat usually successful</td>
<td>Effective</td>
<td>+ + +</td>
</tr>
<tr>
<td>Botulinum toxin injection</td>
<td>Zygomatic, buccal</td>
<td>All</td>
<td>Spasm</td>
<td>Incomplete</td>
<td>Complete</td>
<td>Increased effectiveness</td>
<td>+ + +</td>
</tr>
<tr>
<td>Doxorubicin chemomyectomy</td>
<td>Zygomatic</td>
<td>&gt;50</td>
<td>Spasm and paresis</td>
<td>Less ectropion than with BT, dry eye</td>
<td>Permanent (?)</td>
<td>Increased effectiveness</td>
<td>+ +</td>
</tr>
<tr>
<td>Unilateral surgical myectomy and bilateral blepharoplasties</td>
<td>Zygomatic</td>
<td>&gt;50</td>
<td>Spasm, dermatochalasis, ptosis</td>
<td>Less ectropion than with BT, dry eye</td>
<td>Permanent (?)</td>
<td>Increased effectiveness</td>
<td>+ +</td>
</tr>
</tbody>
</table>

BT, botulinum A toxin.

decade of treatment. In descending order of cumulative cost, the other therapies are ranked as follows: neurosurgical microvascular decompression, orbicularis oculi myectomy combined with other oculoplastic procedures, doxorubicin chemomyectomy combined with botulinum toxin therapy until a satisfactory result has been obtained. Clearly there is a role for the local treatment of hemifacial spasm with orbicularis oculi chemomyectomy in appropriately selected patients.

REFERENCES