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Use of Injectable Spasticity Management Agents in a Cancer Center

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Abstract

Purpose—To analyze the utilization and effectiveness of injectable spasticity medications by the physiatry team at a tertiary referral based cancer center.

Methods—A retrospective review and analysis of patient and injection characteristics were obtained from patients who had received onabotulinum toxin or phenol nerve block injections from December 1, 2007 through January 31, 2012. Out of 3724 physiatry consultations during this period, 20 (less than 1%) different cancer patients received a total of 54 total procedures.

Results—The majority of patients (17/20, 85%) had a positive response to the injection. A positive response to an injection was defined by: 1) if the patient qualified to receive and was given another injection or 2) if there is a record of improvement if they did not receive another injection. 10/20 (50%) patients received only one injection. Of these, 7/10, (70%) reported a positive response to the injected agent. Those with only one injection, tended to live farther away and die sooner. 4/54 (7%) injection procedures resulted in undesirable reported side effects (2 phenol, 2 botulinum toxin). 9/54 (17%) procedures occurred while the patient was on a chemotherapy protocol. All patients were injected at least 1 year out from initial diagnosis.

INTRODUCTION

Onabotulinum toxin is approved by the Federal Drug Administration for a variety of diagnoses including upper limb spasticity and cervical dystonia. Multiple studies have shown the efficacy of botulinum toxin in different populations with central nervous system (CNS) injury including spinal cord injury, stroke, traumatic brain injury, and cerebral palsy. [1–4] Research on the use of phenol nerve blocks for spasticity management dates back decades.[5–7]

Cancer patients can suffer from spasticity and dystonia due to the disease itself and its treatments. The treatment of spasticity and dystonia can include therapy, exercises, splints/

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casts, oral spasticity medications, botulinum toxin injections, neurolytic agents (e.g. phenol) and intrathecal baclofen pumps.

Few papers have focused on the use of botulinum toxin and nerve blocks in the cancer population. Botulinum toxin has been studied for radiation fibrosis syndrome, pain, hypersalivation and trismus.[8–12] There are several studies on the use of botulinum toxin use for chest skeletal muscle spasms in post-mastectomy patients.[13–16] There are no other publications on the use of injectable treatments in a cancer population for spasticity and dystonia. This may be due to the limited availability and underutilization of physiatry services. Unfortunately, physical medicine & rehabilitation is unavailable in many cancer centers.[17] Therefore, spasticity and dystonia injectable interventions are often also unavailable. When available, cancer rehabilitation is often underutilized due to a lack of awareness of its role and potential benefits.[18–21] The purpose of this study is to evaluate the utilization and results of these spasticity management injections in a cancer population.

METHODS

Subjects

A retrospective review of medical records revealed 22 patients who had received onabotulinum toxin or phenol nerve block injections by the physiatry clinic at a referral based tertiary cancer center from December 1, 2007 through January 31, 2012. Of those 22 patients, 20 patients had a history of cancer. 54 total spasticity procedures were performed on these cancer patients.

Procedure

Approval for this study was obtained from the institutional review board. Data was collected by experienced clinicians from therapy notes and medical records. Information obtained included demographic information (date of birth, date of diagnosis, date of death, gender, race, gender, insurance type, distance from hospital), blood counts, primary cancer, cause of spasticity/hypertonia, indication for injection, guidance methods utilized, dosage of agent used, adverse reactions reported, date of last craniotomy, date of last radiation, date of last chemotherapy agent, and prior use of oral muscle relaxants. Information regarding the effectiveness of the injected agent and reasons for not receiving a repeat injection were also obtained. The distance of the patient's residence from the hospital was calculated using Google Maps.

A positive response to an injection was defined by: 1) if the patient qualified to receive and was given another injection or 2) if they did not receive another injection, it was stated in the medical record that an improvement in tone was observed.

RESULTS

Demographics for the patients are listed in table 1. The median days since diagnosis is quite long at 1447 days (range: 377–6279). All patients were at least one year out from their diagnosis.

Table 2 lists characteristics of the patients' medical histories. Most patients had never been on an oral spasticity agent. Five injections occurred while a patient was on an oral spasticity medication. The most common cause of spasticity was due to the brain tumor and its resection.

Table 3 lists procedure characteristics. The only type of botulinum toxin used was onabotulinum toxin. Most patients received onabotulinum toxin without phenol. Some

patients were actively on chemotherapy at the time of their injection. 43/54 procedures occurred while the patient was already in physical and occupational therapy or immediately enrolled in it after the injection. 50/54 procedures occurred in the outpatient clinic.

Table 4 outlines the differences between patients who received multiple injections and those that received only one. It is of note that the majority of these patients did have a positive effect from their spasticity injections (7/10). Those who received only 1 injection are notable for 2 major differences. Many patients only received one injection because they died soon after and/or before they were due for another injection. Also many of these patients lived farther away than their multiple injection counterparts. There were no statistically significant differences between the single injection group and the multiple injection group with regard to mortality or distance from MDACC (p -values 0.650 and 0.326, respectively). Given the large difference in median distance, the lack of statistical significance is likely due to the small sample size. There was a marginally statistically significant difference in overall survival between the single and multiple injection groups (p -value = 0.0589).

9/54 injections occurred while the patients were actively on chemotherapy. The majority of them were on oral chemotherapy (temazolamide). One injection occurred between intravenous lymphoma chemotherapy dosages. One may be concerned regarding infection risk (especially if leukopenic) and/or bleeding risk (if the patient is thrombocytopenic). For our patients, platelet counts within 1 month of injection were as low as 69,000 per microliter. White blood cell counts were as low as 1,900 per microliter. If the patient was on chemotherapy at the time of planned injection, the primary oncologist was asked before proceeding. There were some cases, where the oncologist preferred for us to hold off on the injection (which we honored). However, the answers were variable depending on the oncologist. There are no formal guidelines with respect to the use of botulinum toxin injections and concomitant chemotherapy or minimum blood cell levels. None of the patients injected while on chemotherapy experienced any botulinum toxin/phenol related complications.

DISCUSSION

The purpose of this study was to analyze the utilization and effectiveness of injectable spasticity medications at our tertiary referral based cancer center. While this study portrays experiences only at our institution, this descriptive study illustrates the experiences of managing a cancer population with spasticity using injectable agents. The treatment of these patients' spasticity was fairly standard. Many patients had received oral spasticity agents in the past and most were also receiving physical and occupational therapy. The results of this study suggest that spasticity management injections are effective when given to these patients. 17/20 (85%) patients had a positive response. Half of the patients (10/20, 50%) received multiple injections strongly suggesting that the first injection was effective. Also most patients who only received one injection also had reports of improvement in their tone (7/10, 70%). Response to the injection is dependent upon a number of factors including the skill of the injector, guidance methods used, and using adequate dosages of botulinum toxin. Randomized placebo controlled trials with spasticity measurements and multiple injectors are needed to better define its effectiveness in this population. The majority of patients had few reported adverse effects to the injectable agent. Bakheit et al. in a randomized, double blind, placebo controlled trial of botulinum toxin type A in non-cancer stroke patients with spasticity reported adverse reactions in 16/27 patients. This, however, was not higher than placebo (20/32).[22] Excessive muscle weakness in the injected area has been reported as high as 6–11% in non-cancer cervical dystonia patients.[23] Neuropathic sensory discomfort has been reported in 9% of lower extremity nerve block non-cancer patients.[24] Only 8/20 of our patients had ever taken oral spasticity agents. Oral spasticity medications are less

successful in treating spasticity in cerebral injury than in spinal cord injury.[25, 26] This is primarily due to the significant sedating effects of these medications in patients who already have cerebral compromise. Most of our patients had a brain injury and most never received a trial of oral spasticity agents.

From our 607 bed cancer hospital, having only 20 different cancer patients injected and 54 total injection procedures over a 4 year period seems quite low. During that same time period our physiatry service received 3724 consultations. This may be explained by a number of factors. First, we have anecdotally observed that the incidence of spasticity in our cancer population is quite low especially in comparison to our colleagues who primarily treat other CNS injury etiologies. It has been reported between 19 and 39% of stroke,[27, 28] between 40 and 65% of spinal cord injuries,[29–31] and 34% of traumatic brain injury survivors suffer from spasticity.[32, 33] 3724 physical medicine & rehabilitation (PM&R) consults (921 from neuro-oncology and neurosurgery) were seen during that time period. Less than 1% of all patients referred to PM&R received an injection. All of the patients injected had had cancer initially diagnosed for over a year. This is also interesting considering that the median lifespan for glioblastoma multiforme (the most commonly encountered primary brain tumor in adults) is 15 months.[34] By the time a year has transpired the majority of high grade astrocytoma patients have completed radiation therapy, are actively on some type of chemotherapy, and many have already died. 6/19 (32%) of our patients had a diagnosis of glioblastoma multiforme. Due to the time it takes to develop spasticity, CNS tumor patients should receive regular follow-up by a physical medicine & rehabilitation specialist. On average, we have 30–40 high grade astrocytoma patients admitted to our inpatient rehabilitation unit each year as well as more on a consult basis. In terms of spinal cord injury, we had no patients with a proven spinal cord injury.

Second, inadequate utilization by oncologic providers of physiatry services is likely a factor. Other research has found physiatry services to be underutilized for cancer patients.[18–21] This could be due to poor awareness regarding the availability of physiatry treatments. Also the cancer and its treatment get the focus from referring oncologists. Consequently, less attention or importance is given to other symptoms such as spasticity. At our institution, attempts have been made to educate referring services regarding the availability of injectable spasticity medications by physiatry and to remind them to identify spasticity when present. As cancer survivor numbers continue to grow, more attention should be placed on residual symptoms such as spasticity.

Finally, another likely contributor is the large proportion of patients who only receive one injection (10/20, 50%). Table 4 sheds some light on possible reasons for this. Many of our patients come from long distances to seek care at our institution primarily for management of their cancer not rehabilitation needs. We suspect that many patients with spasticity are treated by local clinicians. Another issue is the mortality that we encounter working in a tertiary cancer center. Some of the patients died by the time they were due for more injections.

Many of the limitations of this study are due to its design. This is a retrospective study meant to familiarize the reader with what we have experienced at our institution. There is little published research regarding spasticity management in the cancer population. An insufficient number of patients had spasticity severity scores such as the Modified Ashworth Scale available for our study. The small sample size prevents us from performing a number of possible further analyses including the effectiveness of these agents on different brain injury etiologies. Further research is needed in this area.

CONCLUSION

Physiatry can offer effective treatments that are not otherwise available at many cancer centers including phenol and botulinum toxin injections. Despite a small percentage of patients receiving these injections, overall they appear to be safe and effective. These injections are useful and should be available to cancer patients. When available, cancer specialists should be educated on the potential benefits of these medications for their patients.

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Table 1

Demographics

At initial injection	
Median Age	49 years
Median Days Until Death (of deceased patients)	152 days
Median Days Since Diagnosis	1393 days
Median Distance from Hospital	21.8 miles
Race/Ethnicity	
Caucasian	15
African American	2
Hispanic	2
Asian	1
Gender	
Male	14
Female	6
Alive/Deceased	
Alive as of 2/1/2012	13
Deceased as of 2/1/2012	7
Marital Status	
Married	11
Divorced	4
Single	4
Widowed	1
Insurance of Patients	
Medicare	7
Private Insurance	13

Table 2**Medical History of Patients**

Non-injectable Oral Spasticity Agents ever used (just patients)	
Oral Baclofen	4
Clonazepam	1
Cyclobenzaprine	1
Lorazepam	1
Tizanidine	1
Never	12
Intracranial Cancers:	
Glioblastoma Multiforme	6
Low Grade Astrocytoma	1
Oligodendroglioma	4
Meningioma	2
Ependymoma	1
Metastatic Melanoma to brain	1
Other Cancers:	
Breast	2
Lymphoma	1
Ovarian	1
Oral Squamous Cell Carcinoma	1
<u>Causes of Muscle Spasms</u>	
Brain Tumor & Resection	13
Cerebrovascular Accident	4
Sternotomy related muscle spasms	1
Radiation Late Effects	1
Unknown	1

Table 3

Characteristics of Spasticity Injections

Agents Injected	
Onabotulinum Toxin Only	39
Phenol Nerve Block Only	10
Onabotulinum Toxin & Phenol	5
Indication for Injection	
Spasticity	39
Cervical Dystonia	5
Cervical Dystonia & Spasticity	10
Guidance Utilized	
Electromyogram alone	21
Electrical Stimulation alone	12
Both	21
Time since craniotomy	
Less than 1 year	11
Greater than 1 year	29
Never	14
Time since chemotherapy	
Actively on chemotherapy	9
Less than 1 year	9
Greater than 1 year	25
Never	11
Time since radiation	
Less than 1 year	9
Greater than 1 year	36
Never	9
Reported Adverse Effects	
Phenol Nerve Block Dysesthesias	2/15
Onabotulinum Excessive Weakness in Limb	1/49
Onabotulinum URI symptoms	1/49
Mean Onabotulinum Toxin Used	540.0 Units
Average Number of Procedure Visits per patient	2.57
Median Number of Procedure Visits per patient	2
Mean Platelet Count within 1 month of injection (Range Lowest-Highest)	180.4 (69–334) K/UL
Mean WBC Count within 1 month of injection (Range Lowest-Highest)	5.99 (1.9–16) K/UL

URI: Upper Respiratory Infection symptoms, PM&R: Physical Medicine & Rehabilitation, WBC: White Blood Cell, K: thousand, UL: microliter

Table 4

One Injection versus Multiple Injections Patient Characteristics

	Only Received 1 injection n=10	Received Multiple Injections n=10	p value
Deceased	5/10	3/10	0.650 [*]
Median time until death of deceased patients	106 days	254 days	
Survival rate at 1 year	0.3733	0.7778	0.0589 ^{***}
Median Distance	40.0 miles	18.55 miles	0.326 ^{**}
Glioblastoma Multiforme	3/10	2/10	
Oligodendroglioma	2/10	2/10	

^{*} of the deceased patients, Fisher's Exact Test

^{**} Kruskal-Wallis test

^{***} Logrank test for equality of curve