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# Long Term Effects of Intra-articular Botulinum Toxin A for Refractory Joint Pain

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**The purpose of this case series review is to describe our 12 month clinical experience with intra-articular injections of Botulinum toxin Type A (BoNT/A) for refractory joint pain. Eleven patients with chronic arthritis who had failed treatment with oral and/or intra-articular medications and were not surgical candidates were referred to us for management of moderate to severe refractory joint pain in 15 joints. The use of BoNT/A to treat joint pain is a non-FDA approved "off label" treatment with potential side effects. After a detailed explanation of the joint injection procedure, signed informed consent was obtained for the procedure. Fifteen joints were injected with BoNT/A (Allergan, Inc): six lower extremity joints (3 knees, 3 ankles) with 25-50 units and nine shoulders with 50-100 units. Patients were followed for one year or longer. Maximum relief of pain was measured by comparing baseline pain on a numeric rating scale (0-10) to pain at the time of maximum relief (paired *t*-test). Maximum improvement in function was assessed using paired *t*-tests for improvement in active flexion and abduction for the shoulder joint, and by the time to perform sit to stand ten times (the timed stands test, TST) for the lower extremity joints.**

**Results: Two patients were female and nine were male, aged 42-82 years. Five had osteoarthritis (OA), five had rheumatoid arthritis (RA) and one had psoriatic arthritis. All patients were on analgesic and/or anti-inflammatory medications and all joints had previous intra-articular steroid or viscosupplement injections with inadequate or unsatisfactory benefit. A clinically and statistically significant improvement was noted after IA-BoNT/A injections. The mean maximum decrease in lower extremity joint pain was 55% ($p$ =0.02) and the 36% ($p$ =0.044) improvement in the Timed Stands Test was noted at four to ten weeks after injection. There was a 71% mean maximum reduction in shoulder pain severity from 8.2 ± 1.1 to 2.4 ± 1.9 ($p$ <0.001). Active range of motion increased 67% in flexion (from 67.8 ± 27.6 to 113.3 ± 46.6 degrees, $p$ =0.001) and 42% in abduction (from 50 18.5 degrees to 71.1 ± 23.1 degrees $p$ =0.01). No immediate or delayed adverse effects related to BoNT/A were noted after the injection. Duration of pain relief was variable and ranged from 3 to 12 months. Five joints were re-injected with IA-BoNT/A and had a similar decrease in joint pain that lasted 3 to 12 months. Conclusions: This is the first report of the long term effects of intra-articular BoNT/A injections to treat chronic joint pain and the efficacy of repeated injections. Although this study was small, and uncontrolled the results suggest that IA-BoNT/A injections are an effective and safe treatment for chronic joint pain disorders.**

*Keywords:* Botulinum toxin type A; Intra-articular injection; Joint pain

## INTRODUCTION

Joint pain is a significant problem for the more than 20 million Americans with osteoarthritis (OA) and 2.5 million with rheumatoid arthritis (RA) (American Pain Society, 2002; Mahowald, 2004). Chronic knee pain and associated disability, affecting up to 20% of the adult population (McAlindon *et al.*, 1992; Ettinger *et al.*,1994), is a major cause of morbidity, physical limitation and increased health care utilization (Hochberg, 2003). Shoulder pain is very common, especially in the elderly (Bergenudd *et al.*,1988; Bjelle, 1989;

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Chakravarty and Webley, 1990; Chard *et al.*,1991; Miller, 1993), and is also associated with functional limitations (Reeves, 1975; Binder *et al.*,1984; Shaffer *et al.*,1992; Vecchio *et al.*,1995; van der Heijden *et al.*,1996), and poor quality of life (Chard *et al.*,1988; Gartsman, 1993; Matsen *et al.*,1997). Overall, approximately 34 million adults suffer from chronic pain that causes substantial impact on quality of life and costs $100 billion annually (Thornhill, 1997; Dionne and Witter, 2003). The goals of local and systemic therapy for arthritis joint pain are to reduce pain and maintain or improve function (Blomqvist *et al.*, 2000). Oral analgesics have substantial limitations because they may not provide sufficient joint pain relief and often produce intolerable drug side effects and adverse drug interactions (Mahowald, 2000; 2004). These limitations of systemic analgesics has prompted the use of localized intra-articular (IA) treatments with corticosteroids and viscosupplements (Adebajo *et al.*,1990; American College of Rheumatology, 2000). IA therapies may reduce pain, however, the duration of effect is variable. Surgical treatment for refractory joint pain includes arthroscopic lavage and debridement when medical therapies fail. An estimated 650,000 arthroscopies are performed annually at an approximate cost of $5000 each and the benefits of these procedures are being debated (Moseley *et al.*, 2002). Total joint replacement surgery ultimately becomes the only treatment option for refractory joint pain. However surgery may not be appropriate if the individual is too young or is too old and has high risk co-morbid conditions. Therefore, there is a need for a treatment that reduces chronic joint pain and improves function yet avoids toxic effects of systemic therapy and the morbidity and mortality risks of surgery. Such therapy would be a particular benefit for elderly patients. One such option for these patients may be the IA application of botulinum neurotoxin type-A (BoNT/A).

BoNT/A is an effective treatment for painful movement disorders, spasticity, myofascial pain and conditions with increased muscle tone, abnormal posturing, and pain (Brin *et al.*,1988; 1999; Dykstra and Sidi, 1990; Jankovic and Schwartz, 1990; Brashear *et al.*, 2002; Lang, 2002; 2003; Rowland, 2002). The analgesic effects of BoNT/A were initially attributed to the decreased muscle tone and improved head or limb posture. Later studies demonstrated that the analgesic effects of BoNT/A occurred earlier and to a greater degree than the decreased muscle tone, leading to speculation that the neurotoxin may have effects on other systems beyond the neuromuscular junction (Jankovic and Schwartz, 1990; Brin 1997; First, 2000; Alper and Lewis, 2002; Arezzo, 2002). We recently reported our initial experience with the early effects of IA injections of BoNT/A for refractory joint pain due to chronic arthritis (Singh *et al.*, 2004; Dykstra *et al.*, 2005).

The purpose of this report is to describe duration of pain relief following IA-BoNT/A and the efficacy of repeat IA-BoNT/A for refractory joint pain. These 12 month observations suggest that IA-BoNT/A has a variable duration of action and is effective upon repeat injection, thus supporting our conclusion that IA injection of BoNT/A may provide an important new alternative for the treatment for refractory joint pain especially in the frail elderly patients.

## METHODS

### Patients

Moderate to severe joint pain due to chronic arthritis (OA, RA and psoriatic arthritis) that was refractory to oral and/or intra-articular corticosteroids or viscosupplement was evaluated in 11 patients with 15 painful joints. These patients were not candidates for surgical treatment because of age, complicating co-morbid conditions, and/or technical factors that limited surgical options (*e.g.*, nonreparable rotator cuff damage). We gave a detailed explanation that IA injections of BoNT/A is a non-FDA approved "off label" use. We explained the potential risks of an IA injection, and the known side effects of BoNT injections before each subject gave written consent for the procedure. Eleven patients (9 men and 2 women) had 15 joints injected with BoNT/A: 3 knees, 3 ankles and 9 shoulder joints. Six lower extremity joints (3 knees, 3 ankles) were injected with 25 to 50 units of BoNT/A. The patients who had lower extremity IA-BoNT/A were aged 42-54 years. Two joints had RA, three had OA, and 1 had psoriatic arthritis for 3 to 30 yrs. Six frail elderly patients, ages 62 to 82, had severe chronic pain in nine shoulders. Three patients had RA and two had OA for 10 to 30 yrs. The Human Studies IRB at the Minneapolis VAMC approved this retrospective case series review.

The knee joint was injected by inserting the needle 1/2 cm posterior to the medial or lateral aspect of the patella at the junction of the upper 1/3 and lower 2/3 of the patella and advancing the needle in a horizontal plane underneath the patella anterior to the femoral condyles. The shoulder joint was injected using the posterior approach by inserting the needle one cm distal to the posterior corner of the acromion and advancing the needle anteriorly and superiorly until the needle entered the posterior capsule at 1.5 to 1 3/4 inches depth. The ankle joint (tibiotalar) was injected by inserting the needle 1 cm anterior to the distal medial malleolus and advancing the needle posteriorly

and slightly superiorly toward the middle of the ankle joint above the talus.

One hundred units of BoNT/A (Allergan, Inc, Irvine CA) was reconstituted in 1 cc preservative-free 0.5% bupivicaine (Abbott Labs, North Chicago, IL). Joint analgesia within 5 minutes from bupivicaine validated correct IA needle placement. Outcome measures included changes in joint pain and/or function as routinely assessed in post-injection clinic visits. Pain severity was assessed on a 0-10 numeric rating scale (NRS) (Turk *et al.*,1993). Change in pain is calculated as raw change or percent change (Farrar *et al.*, 2000; 2001). Upper extremity function was determined by measuring the degrees of active flexion and active abduction. Lower extremity function was determined by measuring the time to perform sit-to-stand ten times (the timed stands test TST) (Newcomer *et al.*,1993). Duration of effect of IA-BoNT/A was defined as time following IA-BoNT/A injection until pain severity returned to pre-injection severity level or until patient requested repeat injection. Patient records were reviewed to evaluate duration of effects of IA-BoNT/A for 12 months or longer after the first injection, the effects of repeated injections and the appearance of any articular or systemic adverse effects.

**Statistical Analysis**

Descriptive statistics including mean and standard deviation (SD) are given for demographic and clinical characteristics of the patients. Analyses for pain relief and functional improvement were done separately for shoulder and lower extremity (LE) joints. Because the time course of pain relief was variable, paired student's *t*-tests were used to compare baseline pain to pain at maximal pain relief, maximum improvement in baseline Timed Stands Test (TST) compared to best TST for lower extremity joint injections and maximum improvement in baseline flexion, and abduction to best range of motion for injected shoulder. Results were considered statistically significant if $p$ value was $<0.05$. The analyses were done using SPSS 11.5 (Chicago, IL).

## RESULTS

Patient characteristics, medications and co-morbid conditions are given in Table I. Two patients were female and 9 were male, ages ranged from 42 to 82 years. The underlying joint disorder was OA in five patients, RA in five patients and one patient had psoriatic arthritis. All patients were on analgesic and/or anti-inflammatory medications and all joints had had IA steroid injections with inadequate or unsatisfactory benefit.

All lower extremity joints had palpable swelling and tenderness of the selected joint and two had palpable popliteal cysts. Baseline joint pain severity was rated on a 0-10 scale. Lower extremity function was assessed by measuring the time to perform sit-to-stand 10 times (Newcomber, 1993). IA injection of 25 to 50 units of BoNT/A into the knee or ankle resulted in a clinically significant mean maximum pain decrease from 6.8 (SD 1.2) to 2.9 (SD 2.3, $p=0.018$) or a 55% mean maximum decrease in joint pain. (Table II). Five of the six lower extremity joints had 30% or greater pain reduction and 3 of the 6 had 50% or greater pain relief (Table I). The TST improved from 30 seconds (SD 15s) to 17 seconds (SD 14s, $p=0.038$), a 36% mean maximum improvement in lower extremity function. Patient A (Table I) had paraparesis due to an epidural abscess and was unable to perform wheel chair transfers because of the knee pain. Two weeks after the IA-BoNT/A injection he was able to perform a sit-to-stand transfer independently and walk about his apartment using a walker.

Nine painful shoulder joints in 6 patients were injected with 50-100 units of BoNT/A (Table III). Shoulder joint pain severity decreased from 8.2 (SD 1.1) to 2.4 (SD 1.9, $p<0.001$) representing a highly clinically significant 71% mean maximum decrease in shoulder pain severity. All shoulder joints had >30% pain relief and 7 of 9 had 50% or greater pain relief. A clinically significant 67% improvement in active flexion (from 68 degrees, SD 28; to 113 degrees, SD 47degrees; $p=0.001$) and 42% improvement in abduction (from 50 degrees, SD 19 degrees; to 71 degrees, SD 23 degrees; $p=0.01$) was noted at followup.

For the whole group of injected joints, 14 of 15 joints had 30% or greater pain reduction and 10 of 15 joints had 50% or greater pain reduction. The time to onset of joint pain reduction ranged from 2 to 14 days, mean 5.6 days (SD 3.0 days), and maximal pain relief occurred between one week to 3 months after joint injection. IA-BoNT/A appeared to be safe; there was no increase in joint pain or swelling, no periarticular muscle weakness, numbness or dysesthesias in the region of the injected joint. No patient had adverse systemic effects of fever or fatigue during the 2-4 weeks following BoNT/A injection.

The patients in this case series were monitored for 12 months or longer after IA-BoNT/A injections to determine the long term safety and efficacy of IA-BoNT/A. Duration of pain relief from IA-BoNT/A was calculated as the weeks from first injection to return to baseline pain severity, patient request for re-injection or to date patient was lost to follow-up.

Seven patients who had 9 joints injected were lost to follow-up during the 12 months after IA-BoNT/A injections (see Tables II and III for details); three of

these patients died from complications of comorbid illnesses and two patients were admitted to psychiatric facilities because of suicide behaviors.

The long term effects of IA-BONT/A were similar for both lower extremity joint injections and shoulder joint injections. The duration of pain relief was variable and ranged from 3 to more than 12 months. Pain relief was sustained for six months or longer in 4 shoulder joints and 4 lower extremity joints. There were 6 requests for repeat shoulder injections: 4 had second injections and 2 had 3 injections during the 12 months. One knee joint had a second injection. Repeat IA-BoNT/A injections

Table I Patient Characteristics

| Age & Gender | Diagnosis & Joint | Duration | Co-morbidity Conditions* | Co-morbid Score** | Concomittant Medications*** |
|---|---|---|---|---|---|
| A 54 M | OA knee | 4y | SCI, cirrhosis, Hep C, leg ulcers, dep | 12 | Op, gab,aten, las,rab,sert |
| B 42 F | RA knee | 3y | PTSD. OP dep, suicidal | 12 | Op, En, HCQ, P, Nap,rab, cit, lor |
| C 53 M | PsA knee | 10y | BOO, HT, dep, OSA | 13 | MTX, P, Et, dy, metop, pax |
| D 48 F | RA ankle | 30y | COPD, GERD, OP | 8 | Op ,MTX, En, Rab, Su, |
| E 44 M | OA ankle<br>OA ankle | 25y<br>25y | ADD, TBI, TKR ,dep suicidal | 7 | Op, Ibu, flu |
| F 82 M | RA L shoulder<br>RA R shoulder | 30y<br>30y | Falls, hip fx THR, COPD, AF, HT,dement malnutrition | 20 | Op, MTX, gab, Dilt coumadin |
| G 78 M | RA R shoulder<br>RA L shoulder | 18y | DM, GERD, HT | 11 | Op, Ib, Su, Met, Rab, lis, Gly, Hy |
| H 62 M | OA R shoulder | 40y | SCI, ADD, dep amputee, DM, GI bleed, anemia, nephro osteomyelitis | 24 | Op, rab, gly, ins, lor,traz , abx |
| I 75 M | OA L Shoulder | 5y | severe ASCVD, HT, CHF, Gout, DM, dep, THR anemia,uremia, dement, GI bld | 25 | Op, P, metop, hdr , lasix, rab, clopid, clonidine, lor, ins, mert, aml |
| J 77 M | RA Shoulder | 5y | Falls, AS, GI bld, HT | 8 | MTX, Op, P Rab, dilt |
| K 77 M | OA R shoulder<br>OA L shoulder | 5y | LS, TA, OSA, CVA dep osteomyelitis nephrolithiasis | 16 | Op, P,rab, dilt, gab, alp, desip, metop, abx clopid |

*Co-morbid Medical Conditions: SCI-spinal cord injury; Hep C-Hepatitis C infection; COPD-chronic obstructive pulmonary disease; AF-atrial fibrillation; OP-osteoporosis; BOO-bladder outlet obstruction; HT-hypertension; DM-diabetes; GERD- gastroesophageal reflux disease; dep-depression; ADD-addiction disorder; AS-aortic stenosis; LS-lateral sclerosis; OSA-obstructive sleep apnea; dement-dementia/delirium.

**Co-morbid Score: Score on Co-morbidity Questionaire for 15 medical conditions rated 0-3 for present, on treatment, limits activities so range is 0-45. Score reflects overall burden of disease, correlates with SF-36 physical function score, hospitalizations and pharmacy costs. Average score in hospitalized patients was 5.6 (sd4.1) [Sangha O *et al., ArthRheum* (*Arth. Care Res.*) **49**:156, 2002)

***Concomittant Medications: Op=opioids; gab=gabapentin; MTX=methotrexate; P=prednisone; En=Etanercept; HCQ=hydroxychloroquin; Nap=naproxen; Et=etodolac; Ib=ibuprofen; Su=sulindac; Met=metformin; in=insulin; rab=rabeprazole; lis=lisinopril; Gly=Glyburide; metop=metoprolol; hydr=hydralazine; dilt=diltiazem; dy=dyazide; pax=paxil; mert=mertazipine; lor=lorazepam; alp=alprazolam; clopid=clopidrogel; des=desipramine; traz=trazodone; abx=antibiotics; sert=sertraline; hy=hydrochlorthiazide; cit=citalopram; las=lasix; ran=ranitidine; flu=fluoxetine.

also produced significant reduction in joint pain from 7.3 to 2.1 (FIG. 1). Duration of pain relief after repeat injections lasted from 3 to 8 months.

Numerous medical or surgical problems occurred during the 12 month period of observation in this complex group of patients with multiple co-morbid conditions and frailty that had rendered them too high risk for reconstructive joint surgery (see Tables II and III for details). None of these medical problems were determined to be related to the IA-BoNT/A injections.

## DISCUSSION

This is the first report of long term effects of IA injection of BoNT A for refractory joint pain. The mean maximum decrease in pain after the first IA-BoNT/A injection was 55% for lower extremity joints and 71% for shoulder pain and 71% following repeat injections. This degree of pain reduction was both statistically and clinically significant in a group of patients who had failed standard therapies and who were not suitable candidates for reconstructive surgery. This pain reduction was also accompanied by an important improvement in limb function.

In long term follow-up, the joint pain reduction lasted from 3 to 12 months after the first injection and 3 to 8 months after repeat injections. Repeat IA-BoNT/A injection also produced significant and clinically important joint pain reduction. There were no systemic or local adverse side effects from the repeat BoNT/A injection. Whether these changes translate into improved quality of life remains to be demonstrated in a prospective clinical trial.

There are several important limitations to our study that merit comment. This is a case series review of open label, non-randomized treatment allocation. Therefore, our observations are subject to patient and observer (physician) bias. However the improve-

Table II Change in Pain During 12 months after IA-BoNT/A Knee and ankle Injections

| Patient # | #1 | #2 | #3 | #4 | #5 | #5 |
|---|---|---|---|---|---|---|
| Joint | Left knee | Left knee | Right knee | Left ankle | Left ankle | Right ankle |
| Units | 40 | 30 | 20 | 50 | 50 | 50 |
| Baseline Pain level on 0-10 scale | 8 | 7 | 8 | 8 | 5 | 6 |
| Time to onset of pain relief | 6 days | 2 days | 1.5 days | 2.5 days | 14 days | 14 days |
| Early Effects (pain level) | 1w=6 | 1w=2 | NS | 1w=0.5 | NS | NS |
| 1 to 3 months (pain level) | NS | NS** | 1m=5<br>2m=4.5 | 3m=0.5 | 6w=3.5<br>3m=6 | 6w=3.5<br>3m=5 |
| 4 to 6 months (pain level) | 6m=6 | 5m=6 | 6m=3.5 | NS | 4m=4 | 4m=4 |
| 7 to 12 months (pain level) | 11m=7 | 8m=7 | 9m=3.5<br>12m=6 | 13m=0.5 | 9m=7 | 9m=7 |
| Pain level at Maximum effect (%decrease) | 1w=6<br>(-25%) | 1w=2<br>(-71% ) | 6m=3.5<br>(-56% ) | 1w=0.5<br>(-94%) | 6w=3.5<br>(-30%) | 6w=3.5<br>(-42%) |
| Duration of effects | 6mo* | 6mo | 12mo | 13mo | 4m*** | 4m |
| Re-injected | Not requested | At 10 mo 100 units | Not requested | Not requested | Not Requested | Not Requested |
| Pain level | | 6.5 | | | | |
| Pain level at Maximum effect (%decrease) | | 3m=3<br>(-58%) | | | | |
| Duration | | 12mo pain=5 | | | | |

*Patient #1 - died of end stage liver disease due to Hepatitis C and alcohol 12mo after IA-BoNT/A
** Patient #2 - hospitalized for urosepsis 3 months after IA-BoNT/A, missed clinic appointment
***Patient #5 - lost to followup after 4 months, admitted to psychiatric facility for suicide attempt
NS = not seen

Table III Change in pain over 12 months after IA-BoNT/A Shoulder Injections

| Patient # | #1 | #1 | #2 | #2 | #3 | #4 | #5 | #5 | #6 |
|---|---|---|---|---|---|---|---|---|---|
| Shoulder | right | Left | Right | Left | Right | Right | Right | Left | Left |
| Units Injected | 50 | 100 | 50 | 60 | 100 | 100 | 100 | 100 | 75 |
| Baseline Pain Severity level | 7 | 6 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 9.5 | 6 |
| Time to Onset Pain Relief | 2.5 days | 2.5 days | 3 days | 3 days | 5 days | 10 days | 7 days | 7 days | 14 days |
| Early Effects (pain level) | 1w=2 | 1w=0.5 | 1w=5 | 1w=5 | 1w=4.5 2w=3 | 1w=8.5 2w=3 | 1w=3.5 | 1w=3.5 | 1w=6 |
| 1 to 3 months (pain level) | 1m=4 3m=0.5 | 1m=1.5 | 3m=5 | 2.5m=5 | 1m=0 2m=3.5 | 1m=2.5 | 2.5m=4 | 2.5m=4 | 1m=0 |
| 4 to 6 months (pain level) | 6m=6 | 5m=6 | 4m=6 | 4m=6 | 3m=8 | 3m=5 | 5m=6 | 5m=0 | 3m=0 |
| 7 to 12 months (pain level) | 9m=7 | 8m=7 | NS** | NS** | | | 12m=8 | 12m=0 | NS |
| Pain level at Maximum effect (% pain decrease) | 1w=2 (-71%) | 1w=0.5 (-92%) | 1w=5 (-44%) | 1w=5 (--44%) | 1m=0 (-100%) | 1m=2.5 (-75%) | 1w=3.5 (-59%) | 5m=0 (-100%) | 1m=0 |
| Duration of pain decrease | 8mo | 8mo | 4mo | 4mo | | 3mo | 10mo***** | 10mo***** | 3m****** |
| Time of Re-injection | At 10 mo | At 9 mo | no | no | At 3 mo 100 units | At 3 mo 100 units | no | no | no |
| Pain Level at re-injection | 7 | 7 | | | 8 | 5 | | | |
| Pain level at Maximum effect (% pain decrease) | 1w=3 (-57%) | 1w=3 (-57%0 | na | na | 3m=2.5 (-69%) | 1m=0 (-100%) | na | na | na |
| Duration | >3mo* | >3mo* | | | 7mo*** | 8mo**** | | | |

*Patient #1 was lost to follow up in a Nursing Home after 13 months of followup

**Patient #2 died of pneumonia in a Nursing Home at 6 months of followup

***Patient #3 had a third IA-BoNT/A but was lost to followup in Hospice program for end stage renal failure and severe heart failure, he died 18 mo after first injection.

****Patient #4 had a third IA-BoNT/A at 11 months after second IA-BoNT/A and pain decreased from 10 to 0 at 2months after third injection and pain was 5 at 10 month.

*****Patient #5 was lost to followup when he went to a Nursing Home at 10 months of followup.

******Patient #6 did not return to clinic after the 3 month evaluation.

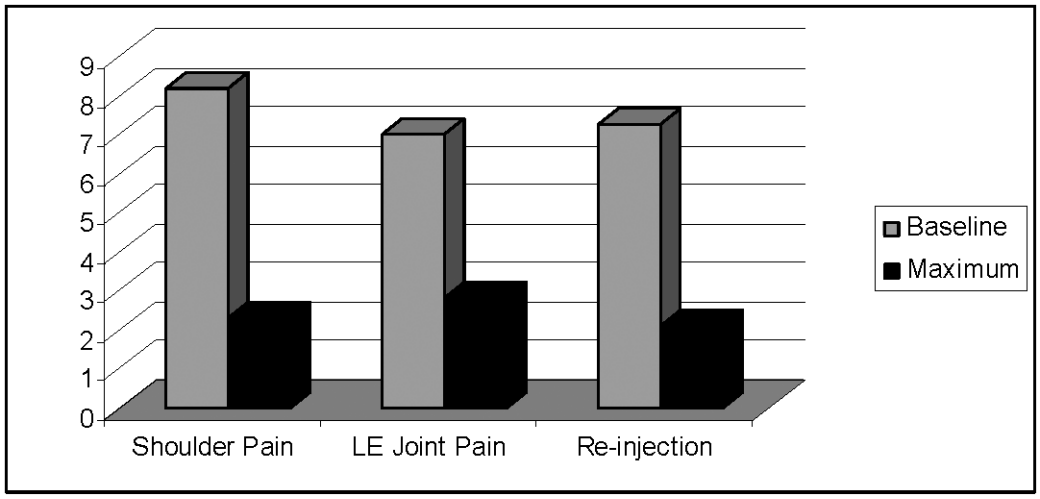


FIGURE 1 Change in Joint Pain after First and Repeat IA-Botox/A Injections. Mean baseline pain (on zero to 10 numerical rating scale) and mean joint pain at point of maximal pain relief after initial IA-BoNT/A injections into 9 shoulder joints and 6 lower extremity joints. Mean joint pain before after repeat IA-BoNT/A injections in 5 joints (one knee and 5 shoulder joints).

ment in the observable measures of function are more objective than subjective pain report, and may be less susceptible to the unblinded bias effects. The refractory moderate to severe joint pain was caused by advanced joint disorders and therefore the results cannot be generalized to patients with mild joint pain or non-specific myofascial joint region pains. Formal dose ranging studies need to be performed as the doses of BoNT/A injected were not standardized for this initial clinical experience with IA-BoNT/A injections. Since this is a small number of injected joints followed for only 12 months, uncommon or rare side effects probably would not have been detected.

Despite these limitations, the results of this study should be put into the context of currently recommended therapies for chronic refractory joint pain. Non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, narcotics, physiotherapy, corticosteroid injection and surgery are recommended for the treatment of chronic joint pain (Berry *et al*, 1980; Mena *et al.*, 1986; White *et al.*, 1986; Petri *et al.*, 1987; Adebajo *et al.*, 1990; van der Windt *et al.*, 1995a; Mahowald, 2000; 2004). Results from these therapies may not be optimal because of adverse side effects, small amount of benefit, and/or short duration of effects (van der Windt *et al.*,1995b; Clements and He, 1997; Thornhill, 1997; Ytterberg *et al.*,1998; Green *et al.*, 2003a,b; Hochberg, 2003; Mahowald *et al.*, 2003a,b).

The efficacy of physiotherapy in treatment of shoulder disorders is not well proven, with a very few exceptions (Van der Heijden *et al.*, 1997; Green *et al.*, 2003b). A systematic review of randomized clinical trials of steroid injections for shoulder disorders found scarce evidence in favor of efficacy of corticosteroids (van der Heijden *et al.*, 1996). Of the seven trials that compared IA corticosteroids with placebo (Richardson, 1975; Berry *et al.*, 1980; Withrington *et al.*, 1985; Petri *et al.*, 1987; Adebajo *et al.*, 1990; Rizk *et al.*, 1991; Vecchio *et al.*, 1993), only two found steroids to be superior to placebo (Petri *et al.*, 1987; Adebajo *et al.*, 1990) and both of these studies were only 4-weeks long. A recent Cochrane Systematic concluded that the evidence that corticosteroids have an effect on shoulder disorders that is small and not well maintained. Data on long-term efficacy and safety of IA corticosteroids is lacking. Trials comparing effectiveness of physiotherapy and corticosteroid injection for patients with shoulder pain found no significant differences at long term follow up (van der Windt *et al.*, 1998; Winters *et al.*, 1999; Hay *et al.*, 2003). Given this lack of effective treatments for refractory joint pain and our promising study data, IA-BoNT/A may provide a new treatment option.

Clostridium botulinum serotype-A, is a zinc dependent endopeptidase, di-chain molecule, comprised of a 100 kD chain which is involved in binding and membrane translocation, and a 50 kD chain that cleaves important molecules involved in mediating neurotransmission (Simpson, 1981; Schiavo *et al.*, 1992). When injected into a muscle, BoNT/A binds irreversibly to specific receptors on nerve terminal membranes and is internalized as an endosome in the cytosol of the nerve ending (Schantz and Johnson, 1992). Within the nerve ending, BoNT/A interrupts neurotransmitter release by cleaving the 25-kD synaptosome-associated protein (SNAP-25) that is involved in synaptic vesicle docking and fusion to the plasma membrane for subsequent release of neurotransmitters (Schiavo *et al.*, 1993; Montecucco and Schiavo, 1994; Montecucco *et al.*, 1996). The proteolysis of these membrane-associated proteins inhibits release of acetylcholine when the nerve is depolarized

and thereby blocks neurotransmission at the motor end plate (*i.e.*, functionally deactivating the neuromuscular junctions by chemodenervation) (Dolly *et al.*, 1990; Dolly, 2003). BoNT can denervate cholinergic sympathetic and parasympathetic neurons and affect autonomic functions including salivation, sweating, heart rate and vasodilatation. BoNT is also thought to inhibit release of other mediators involved in nociception such as substance P, calcitonin gene related peptide (cGRP) and glutamate (Purkiss *et al.*, 1997; 2000; Welch *et al.*, 2000; Cui *et al.*, 2002; 2004; Aoki, 2003; Durham. 2003). The earliest *in vivo* evidence was in a rat carrageenan model of inflammation in which pre-treatment of the hind paw of a rat with BoNT/A, resulted in a significant reduction of carageenan-induced edema, suggesting that BoNT/A may have an effect on neurogenic inflammation (First, 2000). These results were confirmed in the formalin-induced model of inflammation in the rat. Pre-treatment with BoNT/A significantly reduced inflammation and inflammatory mediators in the limb and reduced central sensitization in the spinal cord by reducing *c-fos* gene expression and wide dynamic range neuron activity (Cui *et al.*, 2002; 2004). Work with these two animal models suggested that under conditions of inflammation and sustained pain, BoNT/A exerted anti-nococeptive effects by inhibiting release of other vesicle-mediated substances including cGRP, glutamate and substance-P (Arezzoc 2002). IA injection is a non-muscle model of chronic inflammation and pain which may help to elucidate the possible anti-nociceptive effects of BoNT/A that is independent of the neuromuscular junction blocking action in cholinergic alpha motor neurons.

The clinical use of BoNT seems to be ever expanding. Initial use centered on blockade of the neuromusclular junction in cholinergic neurons for conditions with excessive muscular contraction, including FDA-approved uses for strabismus, blepharospasm, hemifacial muscle spasm and cervical dystonia, glabellar lines and hyperhydrosis (Scott; 1981; Brin *et al.*,1987; 1988; 1999; Fagien, 1999; Comella *et al.*, 2000; Relja, 2002; Rowland, 2002). Worldwide clinical use of BoNT/A has expanded to include spasticity (related to cerebral palsy, multiple sclerosis, stroke, spinal cord and brain injury) (Brashear *et al.*, 2002), writer's cramp, spasmodic dysphonia, detrussor sphincter dyssnergia (Dykstra and Sidi, 1990; Dykstra *et al.*, 2003), esophageal sphincter achalasia, papilla of Vater spasm, puborectalis spasm, anal fissure, chronic tension headache and migraine (Wheeler, 1998; Hallet, 1999; Gobel *et al.*, 2001), chronic tennis elbow pain (Keizer *et al.*, 2002) and myofascial pain (Wheeler *et al.*, 1998; Porta, 2000; Lang, 2003) and joint pain (Mahowald, 2004; Singh *et al.*, 2004; Dykstra *et al.*, 2005).

Our preliminary experience with IA-BoNT/A injections for refractory joint pain together with the extended observations and repeat IA-BoNT/A injections indicate IA-BoNT/A may provide a new therapeutic option for patients with refractory joint pain who are unable to undergo surgical treatments. Much work remains to be done, dose ranging studies must be carried out to determine optimal dose and intervals for IA-BoNT/A injection therapy and these initial options must be verified in randomized controlled studies.

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