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Treatment methods for post-traumatic elbow stiffness caused by heterotopic ossification

Christina E. Freibott, MPH*, Henrik C. Bäcker, MD, Seth C. Shoap, BA, BS, Liana J. Tedesco, MD, Samuel E. Galle, MD, Melvin P. Rosenwasser, MD

Department of Orthopaedic Surgery, Columbia University Medical Center/Presbyterian Hospital, New York, NY, USA

Hypothesis: Heterotopic ossification (HO) is a common complication of surgically treated elbow fractures that can inhibit range of motion and impair quality of life. Although there are many treatment methods for HO, there is a lack of consensus as to the best option. We hypothesized that contracture release combined with Botox injection would lead to improved functional outcome scores when compared with current treatment methods.
Methods: A retrospective review was conducted of patients who presented to a single surgeon with HO secondary to elbow fracture between 2005 and 2018. A total of 59 patients were identified who met inclusion criteria. Data were classified into 3 groups: contracture release (control − CR), Botox injection with CR (Botox + CR), and radiation therapy with CR (CR + RT). Range of motion measurements were obtained, including flexion, extension, pronation, and supination.
Results: A total of 30 patients (30 of 59, 50.8%) received CR, 6 (6 of 59, 9.2%) were treated with CR + RT, and 23 (23 of 59, 40.0%) had CR + Botox. There was a significant difference between pre- and postoperative arc of motion for both CR + RT ($P < .01$) and CR + Botox ($P < .01$). In addition, there was a significant difference in pre- and postoperative extension for patients who received intraoperative Botox injections ($P < .05$). There was no significant difference between pre- and postoperative motion nor extension in the CR group.
Conclusion: Intraoperative Botox injection with CR is an effective method in the treatment of post-traumatic elbow stiffness caused by HO.
Level of evidence: Level III; Retrospective Cohort Comparison; Treatment Study

Keywords: Botox; heterotopic ossification; contracture release; radiation therapy

Elbow stiffness after trauma is a challenging and debilitating clinical condition.[4] Post-traumatic stiffness has numerous causes including arthrosis, heterotopic ossification (HO), fracture nonunion, and soft tissue contracture.[2] HO, which is the atypical growth of bone in nonskeletal tissues, can result in pain and clinically important stiffness leading to decreased range of motion (ROM).[8,14,27] Decreased ROM and resultant loss of function can lead to decreased patient satisfaction. Direct trauma to the elbow is associated with an increased risk of heterotopic bone formation, with an incidence of 3% reported for elbow dislocations and 89% for intra- and periarticular fractures with brain injury.[1,10,27] It has been reported in the literature that 86% of patients receiving total elbow arthroplasty have HO.[26] Furthermore, 43% of patients treated operatively for fracture dislocations have been reported to have HO, along with an HO prevalence of 50% in combined olecranon and radial head fractures, 37.5% of type B distal humerus fractures, 33.3% of type A distal humerus fractures, 33.3%

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*Reprint requests: Christina E. Freibott, MPH, Department of Orthopaedic Surgery, Trauma Training Center, 622 West 168th Street, New York, NY 10032, USA.

E-mail address: cef2141@cumc.columbia.edu (C.E. Freibott).

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of terrible triad injuries, and 31.2% of isolated radial head fractures.[14,30]

Current conservative, nonsurgical treatment options include physical therapy, anti-inflammatory medications, and manipulation under anesthesia.[12] Nonsteroidal anti-inflammatory drugs, such as indomethacin, can also be used as a prophylactic for HO by inhibiting osteogenic differentiation of progenitor cells.[24] However, these measures have limited effectiveness in the setting of HO.[19] Surgical options including contracture release (CR), excision of heterotopic bone formation, and adjunctive radiation therapy (RT) have been well documented. However, little consensus and evidence exists with regard to the most effective surgical or adjunctive treatment for post-traumatic HO about the elbow.

Botox is a purified version of Botulinum toxin type A, which is an exotoxin produced by the bacteria *Clostridium botulinum.* Botox has been used for nearly 3 decades in the field of orthopedic surgery for its reliable, safe, and reversible localized muscle paralysis.[29] To date, it has been used in the treatment of lateral epicondylitis,[13,16,18,21] tendon repairs of the hand,[29] chronic low back pain,[7,9,15,20] and as a preventative measure for flexion contractures in both total knee arthroplasty and total hip arthroplasty.[3,28] However, the usage and efficacy in treating post-traumatic elbow stiffness and HO has yet to be studied.

We hypothesize that the adjunctive use of botulinum toxin injections intraoperatively into the biceps and brachialis muscles will break the cycle of pain, co-contraction, and muscular guarding that ultimately lead to limitation of flexion/extension, stiffness, and joint contracture. We posit that Botox injections will allow for early extension and result in increased final ROM with overall improved postoperative patient outcomes.

The purpose of this study was to investigate the efficacy of 3 treatment groups in the treatment of HO in post-traumatic elbow stiffness: CR alone, CR with adjunctive RT (CR + RT), and CR with intraoperative botulinum toxin injection (CR + Botox). CR and CR + RT are both considered standard of care, and thus defined as the control groups, whereas the new CR + Botox therapy was the treatment group.

Materials and methods

Patients

After institutional review board approval, a retrospective review was conducted of patients older than 18 years who presented to a single surgeon with HO secondary to traumatic elbow fracture between 2005 and 2018. Patients less than 18 years of age who did not have HO secondary to traumatic elbow fracture were excluded. A total of 59 patients were identified who met inclusion criteria and had documented pre- and postoperative ROM measurements. Patients either underwent CR, CR + RT, or CR + Botox. All surgeries were performed by the senior author at the same institution.

Treatment

Elbow contracture release

Multiple approaches, including direct posterior, combined medial/lateral, or through previous incisions, were used to visualize the elbow. Complete capsulectomies were performed and, depending on specific indication, included the anterior and posterior sections. Careful subperiosteal dissection along the epicondylar ridges, removal of any loose bodies/foci of HO, and protection of the local neurovascular structures allowed for accurate dissection. Specific releases included the humeral attachment of the pronator teres, the posteromedial collateral ligament, and the brachialis muscle from the medial capsule for later capsulectomy. The anterior oblique medial collateral ligament was carefully preserved universally. Of specific importance, capsulotomies were not performed as the senior author has abandoned this technique because of suboptimal functional long-term outcomes. In all cases, the ulnar nerve was exposed in an anterograde fashion with careful preservation of the accompanying vasovasorum, protected with vessel loops throughout, and transposed on a symptomatic and/or intraoperative anatomical basis. Tourniquet was used throughout each case and hemostasis was obtained with bipolar electrocautery.

Radiation therapy

Preoperative coordination with a radiation oncologist was used when appropriate. Patients were treated with 700 cGy of local elbow joint external beam RT in a single dose within 48 hours postoperatively.

Botox injections

In those indicated cases after the above-noted complete capsulectomy, 100 units of Botox were reconstituted with 2 cc of saline per injection and injected into the bifurcation of the biceps in the upper arm and the brachialis muscle at the elbow joint level (Fig. 1). To avoid injury to the musculocutaneous nerve, direct visualization in the brachialis as well as around the biceps was carried out. Biceps injections were made greater than 13 cm distal to the coracoid process, which has been shown in anatomic studies to be where the nerve enters the muscle belly.[6,9] Brachialis injections were made more than 17 cm distal to the coracoid process in the midline to avoid injury to the medial neurovascular structures and the musculocutaneous nerve.[6,9]

Postoperative rehabilitation

At the conclusion of all operative procedures, a sling and soft dressing (and an occasional anterior splint) was applied with the elbow in approximately 30° to full extension. The arm was well protected in a sling and swathe for 7-10 days. Every patient then began a formal physical therapy program at least 2 or 3 visits per week for ROM and static progressive bracing. A turnbuckle brace (Bledsoe Brace Systems, Grand Prairie, TX, USA) was applied, calibrated to allow full elbow extension and approximately 90° of elbow flexion. For those patients who underwent Botox injection, flexion was performed primarily by the spring action of the brace

Figure 1 Injection sites for Botox.

with some assistance from the supinator and brachioradialis. Patients also performed a home therapy regimen including active ROM of the elbow within the confines of the brace several times daily. For the next 2 weeks, active ROM exercises continue to progress and light resistive exercises were initiated for the forearm, wrist, and hand. Patients were allowed to remove the brace at home for short periods of time, but they remained in the brace during sleep and travel.

All treatment groups underwent the same rehabilitation protocol. Three and a half weeks postoperatively, the patients began strengthening exercises for elbow extension and flexion, beginning with very light weights (1/2 to 1 pound), and in the gravity eliminated position. Gradually, although respecting patient tolerance, these resistive exercises progressed to heavier weights and/or theraband in the against gravity position.

At 6 weeks to 3 months after surgery, the clinical effects of Botox began to wear off and clinical muscle function was observed. These patients discontinued the use of the brace and began using 2 and 3 pound weights for biceps and triceps strengthening. Functional activities and resistive exercises progressed until the patients obtained their maximum rehabilitation potential. Physical therapy continued for at least 6 months after the procedure.

Objective evaluation

We compared pre- and postoperative ROM measurements, including flexion, extension, pronation, and supination, within and between the 3 treatment groups. Flexion and extension were further analyzed as a grouped measurement classified as "arc of motion."

Statistical analysis

Preliminary statistical analysis (analysis of variance test) compared preoperative and postoperative values within each treatment category as well as against the other treatments using Statistical Package for the Social Sciences (SPSS; IBM, Armonk, NY, USA). In addition, a regression (analysis of covariance [ANCOVA]) analysis was conducted of postoperative values on both preoperative values and treatment group.

A paired *t*-test that matched for sex and age (±2 years) was performed in 2 cohorts to analyze the efficacy of treatment: CR vs. CR + Botox vs. CR + RT; and CR vs. CR + Botox alone.

Results

A total of 59 patients met inclusion criteria during the selected time period. The average age was 44 ± 21 years, with 33 (55.9%) being male. The average length of follow-up was 1.61 ± 2.25 years (range: 0.09-8.53 years). Of the 59 patients, 30 (50.8%) received CR alone, 23 (40.0%) underwent CR + Botox injection, and 6 (9.2%) were treated with CR + RT. Initial analysis was conducted including patients from all 3 treatment types and reported average preoperative extension of 43° (range: 0°-110°, standard deviation [SD]: ±26), flexion 103° (range: 0°-135°, SD: ±33), pronation 60° (range: 5°-90°, SD: ±37), and supination 53° (range: 0°-90°, SD: ±33). Postoperative ROM measurements were found to be 18° (range: 0°-35°, SD: ±13) of extension, 125° (range: 100°-140°, SD: ±63) of flexion, 77° (range: 40°-90°, SD: ±23) of pronation, and 67° (range: 28°-90°, SD: ±24) of supination. In terms of average improvement when looking at all 3 treatments, extension improved by 25°, flexion by 22°, pronation by 17°, and supination by 14°. The complete data stratified by treatment group are reported in Table I.

Paired *t*-test

A paired *t*-test was conducted between treatment groups matching for age and sex (±2 years) in 2 cohorts.

CR vs. CR + Botox vs. CR + RT

The data for the case-matched control of all treatment groups are summarized in Table II.

There were significant differences in preoperative flexion-extension arc, with both the CR + Botox ($P = .043$) and CR + RT ($P = .019$) groups being significantly worse than the CR group. In addition, there was a significant difference in postoperative extension between CR + RT and CR ($P = .004$).

When comparing intragroup pre- to postoperative values, there was no significant difference in the CR group for extension, flexion, or arc of motion. There was a

Table I Pre- and postoperative range of motion for all treatment groups

	Preoperative						Postoperative					
	Extension	Flexion	Ex-flex arc	Pronation	Supination	Pro-sup arc	Extension	Flexion	Ex-flex arc	Pronation	Supination	Pro-sup arc
CR	33	107	78	55	40	65	18	124	106	74	64	138
CR and Botox	53	103	50	68	66	134	16	128	104	81	75	156
RT	53	87	34	51	63	114	33	118	85	90	68	158
All groups	46	99	54	58	56	114	22	123	98	82	69	151

CR, contracture release; *RT*, radiation therapy.

Table II Pre- and postoperative range of motion for case-matched CR, CR + RT, CR + Botox

	Preoperative						Postoperative					
	Extension	Flexion	Ex-flex arc	Pronation	Supination	Pro-sup arc	Extension	Flexion	Ex-flex arc	Pronation	Supination	Pro-sup arc
CR	18	113	95	35	35	70	25	130	105	80	63	161
CR and Botox	50	91	41	77	83	160	16	128	104	81	75	150
RT	51	91	41	77	83	160	23	118	96	79	77	156

CR, contracture release; *RT*, radiation therapy.

significant difference in pre- and postoperative arc of motion for both CR + RT ($P = .011$) and CR + Botox ($P = .039$) (Fig. 2).

CR vs. Botox

The results of the paired *t*-test between the CR and the CR + Botox treatment groups are summarized in Table III. When evaluating only CR + Botox vs. CR, there was a significant difference in preoperative extension ($P = .036$), with Botox being significantly worse. There were no significant differences when assessing postoperative values between the 2 groups.

When comparing pre- to postoperative values, patients who underwent CR + Botox had a statistically significant improvement in extension ($P < .001$), flexion ($P = .002$), and arc of motion ($P < .001$). Those with CR reported significant improvement in postoperative flexion ($P = .039$), but none for extension or arc of motion (Fig. 3).

Complications

There were no treatment-related complications in any of the 3 study groups, including reoccurrence of HO.

Regression analysis

Using SPSS, a regression (ANCOVA) analysis was conducted of postoperative values on both preoperative values and treatment group. An ANCOVA is an analysis of covariance that combines analysis of variance and regression models, and was used here to perform a regression of postoperative values on both preoperative values and treatment group. The treatment method was a significant predictor ($P < .05$) of postoperative success. The CR + Botox group demonstrated a significant difference between pre- and postoperative values ($P < .001$), whereas CR and RT did not.

Discussion

HO is a well-documented complication in surgically treated elbow fractures, which can greatly inhibit elbow ROM and significantly impair quality of life. Conservative and operative treatment methods have been discussed in detail in the literature for a variety of age groups and injury mechanisms. Multiple operative techniques, such as CR, heterotopic excision, and adjunctive RT, have been described to alleviate patients' symptoms. Complications of these procedures include recurrence of HO, hematoma formation, infection, and ulnar neuropathy.[5] Although many have proven to be successful, it is imperative to consider an option that will maximize both clinical results and patient-reported outcomes.

CR has been reported with good postoperative and long-term results in restoring ROM. A study conducted by Haglin et al[11] examined ROM and recurrence of HO in 103

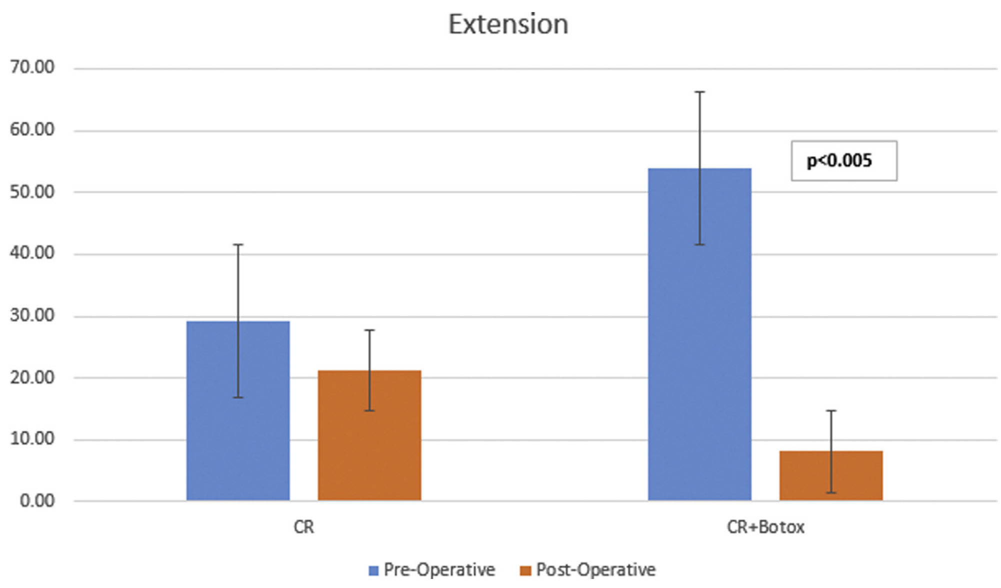

Figure 2 Flexion-extension arc of motion. *CR*, contracture release.

Table III Pre- and postoperative range of motion for case-matched CR and CR + Botox

	Preoperative						Postoperative					
	Extension	Flexion	Ex-flex arc	Pronation	Supination	Pro-sup arc	Extension	Flexion	Ex-flex arc	Pronation	Supination	Pro-sup arc
CR	29	103	74	51	32	82	21	120	99	73	65	138
CR and Botox	54	100	46	74	66	139	8	130	122	79	71	140

CR, contracture release.

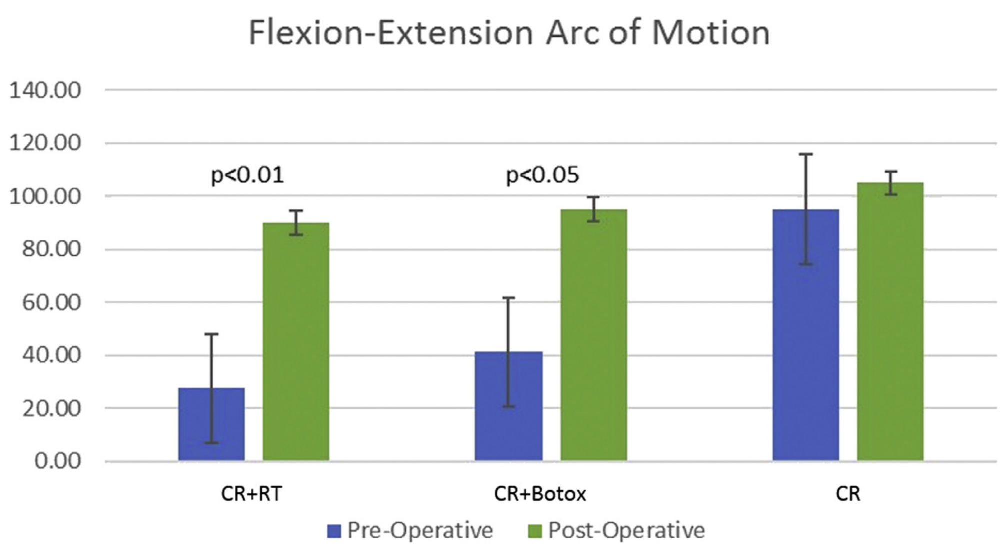

Figure 3 Extension – CR and CR + Botox. *CR*, contracture release; *RT*, radiation therapy.

patients who underwent post-traumatic elbow CR. Similar to our study, they found that CR resulted in a significant increase in elbow flexion; however, they contradicted our findings by determining a significant increase in extension and overall range of motion. In addition, Haglin et al[11] found that HO recurred in 14% of the patients, and 11% of the patients elected to undergo a secondary operation to gain more motion.[26] Another study conducted by Koh et al[17] had similar results. Their retrospective review on 77 surgically treated patients with post-traumatic elbow stiffness caused by HO found that 84.4% of patients obtained a total motion arc of $\geq 100°$, but observed HO recurrence in 20.8% of patients.[27] These studies, among others, support the notion that CR is effective in restoring elbow ROM, but recognize there is room to optimize treatment method to prevent secondary complications and reduce HO recurrence.

Another well documented treatment for heterotopic ossification is RT. This technique is based on the hypothesis that osteoprogenitor cells, which are present in the early stages of HO development, are particularly sensitive to radiotherapy.[23] RT currently plays a large role in preventing HO recurrence in the hip, and its use in this setting is supported by randomized clinical trials. However, little is known in terms of the safety and efficacy for non-hip joints. A standard of care in terms of dosage, timing, and indications for RT in the elbow has yet to be established. There is great variability in dose prescription, with a mean of 816.2 cGy (±242.1), and range of dose per fraction of 200-800 cGy found in the literature.[23] A prospective study by Robinson et al[25] examined 36 patients who underwent elbow surgery followed by a single-fraction RT, 31 of whom had prior elbow trauma. Thirty-four patients received 700 cGy, and 2 received 600 cGy. After a mean follow-up time of 8.7 months, they found that all patients had an improved range of motion from baseline, and 3 developed new HO. Similar to our findings, this study found that RT improved range of motion in patients with post-traumatic HO. Conversely, Ploumis et al[22] conducted a systematic review of 27 studies that used RT for elbow HO. They concluded that there are no high-quality, consistent research findings on the safety and efficacy of RT for elbow HO, and concluded that it should not be used as a first-time treatment of prevention for elbow HO. Safety of RT was not examined in our study. Despite the promising results in postoperative range of motion for the CR + RT cohort, the long-term effects of this therapy are unknown. More research is needed to ensure its safety before it can be accepted as the standard for treating elbow HO. Botox injection therapy has been described in these scenarios, but results have not been documented in the treatment of post-traumatic HO. This study serves to report these data and validate them as an option in treating this complex problem.

Limitations of this work

A limitation of this study is its retrospective nature. A prospective, randomized study should be conducted to eliminate any possible retrospective data analytical bias in our results. Furthermore, a prospective study would allow for analysis at multiple time points, as our project only looks at the final follow-up. In addition, there are only 6 cases of CR + RT included in this analysis, which is significantly lower than the CR and CR + Botox groups. As such, this may skew the data and subsequent interpretation of the results.

In conclusion, Botox is a safe and effective method of treatment in patients with post-traumatic elbow stiffness caused by HO. Future research should consider a large multicenter, prospective, randomized study design to further assess the efficacy of the aforementioned treatment options.

Conclusions

This study demonstrates that the effectiveness of intraoperative Botox injection with CR is an adjuvant method of treating post-traumatic elbow stiffness associated with HO. Favorable outcomes in extension, flexion, and arc of motion were reported in patients treated with Botox injections. Furthermore, patients treated with either RT or Botox injection had better postoperative results than those treated with CR alone.

Disclaimer

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