**CLINICAL EFFICACY AND SAFETY OF INTRA-ARTICULAR BOTULINUM TOXIN A INJECTIONS FOR KNEE OSTEOARTHRITIS – A RANDOMISED CONTROL TRIAL (STUDY PROTOCOL)**

**ABSTRACT**

**INTRODUCTION**

The burden of osteoarthritis (OA) in Australia is growing steadily due to our ageing population, rising rates of obesity and a growth in sports-related injuries.[[1]](#footnote-2) The most recent figures from the Australian Institute of Health and Welfare (AIHW) show that 9.3 percent of Australians have some form of OA.[[2]](#footnote-3) More specifically, knee OA is an increasing issue with the rate of total knee replacements (TKRs) growing exponentially in Australia and other developed countries over the past two decades.[[3]](#footnote-4) The AIHW states a 38 percent rise in TKRs from 2005-06 to 2017-18.[[4]](#footnote-5) The average TKR costs between $19,000 to $30,000 per patient and the total estimated cost of TKRs increased from $448 million to $905 million from 2003 to 2013.[[5]](#footnote-6) It is forecasted that the annual economic burden stemming from TKRs in Australia will sit between $1.38 billion to $3.40 billion by 2030.[[6]](#footnote-7) These figures render it vital that there is new research into non-operative treatment options for knee OA in Australia. This is particularly the case for the younger patient population given the risk of this population requiring multiple revision procedures.

The two primary tenets of treatment for knee OA are (a) alleviation of pain and (b) improvement in function.[[7]](#footnote-8) The general framework for the management of knee OA exists as a multimodal and stepwise approach. The non-operative management options include non-pharmacological interventions, such as exercise, weight loss and bracing, and pharmacological interventions such as oral analgesia, topical analgesia and intra-articular (IA) injections.[[8]](#footnote-9) Several IA injection options have been studied over recent years, including botulinum toxin type A (BTA), corticosteroids (CS), hyaluronic acid (HA), dextrose prolotherapy and platelet-rich plasma (PRP).

IA BTA injections have become a particular source of research interest in the management of knee OA due to an evolving understanding of the various mechanisms of action of BTA.[[9]](#footnote-10) Botulinum toxin (Botox) is produced by the anaerobic bacterium *Clostridium botulinum* and there are seven therapeutic serotypes of Botox ranging from A to G, of which only A and B are used as therapeutics.[[10]](#footnote-11)The pain in OA involves both nociceptive and neuropathic mechanisms and affects both peripheral and central pain pathways.[[11]](#footnote-12)Botox inhibits acetylcholine release into the synaptic cleft cholinergic nerve terminals and thereby causes muscle paralysis.[[12]](#footnote-13) It was originally used in neuromuscular disorders, such as spasticity and torticollis, to relieve pain by inducing muscle paralysis. However, it was noted that the pain-relief from Botox preceded paralysis effects and so other mechanisms of action were investigated.[[13]](#footnote-14) It is suggested that Botox also suppresses excitatory and nociceptive neurotransmitters, thereby reducing peripheral sensitisation but also indirectly acting on central sensitisation.[[14]](#footnote-15)

The mechanisms of action of Botox for OA pain are promising but the clinical evidence for IA BTA injections is still lacking. There have been several randomised control trials (RCTs) assessing the impact of IA BTA injections on pain and function in knee OA. However, the RCTs are often lacklustre due to small sample sizes, short follow-up periods and significant discrepancies in baseline patient demographics.[[15]](#footnote-16) Hsieh et al. published a prospective RCT in 2016 assessing the efficacy of IA BTA 100U injections in knee OA compared to a control group who received education only.[[16]](#footnote-17) Their results showed a significant reduction in pain using the Visual Analogue Scale (VAS) and a significant improvement in function using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) compared with the control group. However, their study was limited by a small sample size (46 participants), single-blinding, a lack of injection placebo and the fact that the IA injections were not administered using ultrasound guidance. Another example is a RCT published by Najafi et al. in 2019 of 30 participants all of whom received an IA BTA 100U injection.[[17]](#footnote-18) Their results showed a significant decrease in pain using the VAS and a significant improvement in function using the Knee Injury and Osteoarthritis Outcome Score (KOOS) from baseline to four weeks. However, this study also had several significant limitations including a very small sample size, lack of control group, absence of participant blinding and a short follow-up period. Nielsen et al. published a study in 2016 exploring the pain mechanism underlying the specific clinical effect of IA BTA injection in patients with knee OA.[[18]](#footnote-19) Participants were split into nociceptive and neuropathic sub-groups and outcomes were assessed using pain biomarkers and clinical pain scores. The results showed no significant difference in pain biomarkers or clinical pain scores across the participants as a whole or in either of the sub-groups. This study had a larger participant group (121 participants) and longer follow-up period (12 weeks) than other studies in this area but it did not assess functional improvement, nor did it look at varying doses of IA BTA.

Several recent RCTs have analysed the efficacy of IA BTA compared with other IA injection therapies. Bao et al. published a RCT in 2018 comparing IA injections of saline placebo, BTA and HA plus therapeutic exercise for all participants.[[19]](#footnote-20) Their results showed that VAS and WOMAC scores improved significantly in the BTA and HA groups but not in the placebo groups at both 4 weeks and 8 weeks post-injection. Interestingly, this study also looked at MRI and x-ray imaging findings post-injection but did not find any difference. Mendes et al. published a RCT in 2019 comparing IA injections of normal saline, BTA and triamcinolone.[[20]](#footnote-21) While the IA steroid injection had the best evolution of results over the 12 week follow-up period, there was no significant difference in pain or function results between groups. Rezasoltani et al. conducted a RCT published in 2020 comparing physical therapy, IA BTA injection, IA dextrose prolotherapy and IA HA injection.[[21]](#footnote-22) BTA and dextrose prolotherapy had the most significant impact on VAS and KOOS scores while HA was the least effective. Finally, Shukla et al. published a RCT in 2018 comparing IA injections of BTA plus triamcinolone versus triamcinolone alone and found that pain scores improved more markedly in the combination IA injection compared with IA triamcinolone alone.[[22]](#footnote-23)

There are also several systematic reviews and meta-analyses on the topic of IA BTA injections in OA pain. However, these too are limited in application as they often compare studies with significant heterogeneity or those looking at IA BTA injections for multiple joints or varying arthropathies. Khenioui et al. published a systematic review on the utility of IA BTA injections spanning a vast range of conditions including OA, adhesive capsulitis and chronic pain post-joint replacement.[[23]](#footnote-24) Courseau et al. published a meta-analysis of RCTs in 2018 which examined the efficacy of IA BTA in painful joint diseases, covering multiple joints and arthropathies.[[24]](#footnote-25) These reviews provide general evidence regarding the utility of IA BTA injections in a broad sense but fail to provide evidence upon which specific management protocols can be based. Zhai et al. published a more recent systematic review and meta-analysis in 2019 which specifically focused on IA BTA in knee OA.[[25]](#footnote-26) The analysis looked at short-term (< 4 weeks) and long-term(> 8 weeks) results and found that there was a significant improvement in pain and function due to IA BTA injections for knee OA. The limitations of this meta-analyses were the small number of studies included and the short follow-up periods of the studies.

The current study aims to address gaps in the current literature in this area by conducting a high quality RCT with the primary aim of assessing the clinical efficacy and safety of intra-articular (IA) botulinum toxin A (BTA)injections in knee OA underpinned by the following hypotheses:

(a) IA BTA injection will significantly reduce pain compared to a placebo injection of normal saline

(b) IA BTA injection will significantly improve function compared to a placebo injection of normal saline; and

(c) There will be no significant difference in adverse events between the BTA and other commonly used intra-articular injections used in osteoarthritis including CSLA and hyaluronic acid .

**METHOD**

**Study design**

* Randomised control trial.
* Single-centre – Albany Hospital (WA) & Royal Perth Hospital (WA)
* Double-blinded.
* Random allocation to one of two treatment groups – botulinum toxin A (100 units) OR 5ml 0.9% normal saline 5ml
* REDCap software to perform the randomisation process.
* Power calculation = 50 patients in each arm.
	+ Mean OKS score 20 with SD 8
		- Based off of study by Beard et al who reviewed clinical applicability and meaningful changes of the oxford knee score system by utilising the NHS database with over 150,000 patients.
	+ Expected mean improvement if BTA showing clinically beneficial OKS ≥5 (Beard et al)

**Inclusion criteria**

* Age ≥ 50 years.
* Diagnosis of knee OA confirmed on clinical exam and radiologically by Kellgren-Lawrence Grading Scale (grade III & IV)
* Symptoms present for ≥ 6 months.
* Ability to understand and participate in the trial.

**Exclusion criteria**

* Age < 50 years.
* Any intra-articular injection in the last 12 months (CS, HA, PRP etc).
* Hx of prior trauma to the knee i.e. fracture, dislocation.
* Neuromuscular disorders e.g. myasthenia gravis, Lambert-Eaton, ALS etc.
* Other knee arthropathy e.g. RA, gout etc.
* Lower extremity dysfunction due to neurological or medical cause e.g. CVA, TBI, diabetic neuropathy.
* Serious coagulation disorders or on anticoagulant.
* Pregnancy / breastfeeding.

**Recruitment**

* Patients referred to Orthopaedic Outpatient Clinic with a diagnosis of primary knee OA (criteria for diagnosis as outlined above)
* Eligible participants invited to participate – education and consent.

**Intervention**

* All injections to be performed under radiological-guidance by a radiologist.
* Joint effusion aspirated prior to injection (if present).
* Group A – BTA 100U reconstituted with 5ml 0.9% normal saline.
* Group B – 5ml 0.9% normal saline
* No restriction will be placed on patients with regards to use of other analgesia medication post intervention and basic information will be collected regarding analgesia use pre and post intervention

**Primary & secondary outcomes**

* Pain assessment using VAS score.
* Function assessment – Oxford Knee Score (OKS) + EQ5D
* Reduction in analgesia requirements from pre-intervention
* Adverse events – adverse event checklist provided to participant based on the literature at each data collection time point – can simply tick ‘yes’ or ‘no’. Can also include a section where participants can describe any other adverse event experienced in free text.

**Data collection points**

* Baseline data pre-injection.
* Short-term data points:
	+ 2 weeks.
	+ 6 weeks.
	+ 3 months.
* Long-term data points:
	+ 6 months.
	+ 12 months.

**Data storage**

* Each participants data will be recorded on a case report form.
* Personal information will be removed and patients will be identified throughout the study through the use of a unique identified code.
* De-identified participant data collected on the case report form will be transferred to a secure electronic database.
* Only approved individuals that are part of the study research team will be allowed access to the database through username and password protection.

**RESULTS**

**General**

* Power of 0.8.
* Intention-to-treat analysis.
* Two-tailed stat tests with α of 0.05.

**Baseline characteristics**

* Reported in a table between groups and analysis to check for sig. differences.
* Age.
* Gender.
* BMI.
* KL grade.
* Pre-injection VAS pain score.
* Pre-injection function score.
* Paracetamol consumption post-injection.

**Primary outcomes**

* Pain & function:
	+ Independent sample T-test to assess differences *between* groups at each data collection time point.
	+ Paired sample T-tests to assess differences *within* groups across the data collection time points.
	+ Sub-group analyses – ANOVA test to assess for differences in pain and function outcome based on KL grade of OA.
* Adverse events:
	+ Presented as a table and split based on non-serious and serious.
	+ Independent sample T-tests to assess difference in overall rate of non-serious and serious adverse events.

**SAFETY**

* Serious adverse events (SAEs) will be reported to the ethics committee and monitored by an independent data monitoring and safety committee.
* Potential adverse events include:
* Haemarthrosis.
* Septic arthritis.
* Botox-specific side effects– muscle weakness / arrhythmia / dysphagia / anaphylaxis / skin rash.

**ETHICS**

* The study will be conducted in agreement with the Declaration of Helsinki.
* The evidence surrounding different IA BTA doses is lacking so allocation to low dose or high dose is ethically acceptable.
* The adverse event rate for IA injections and for IA BTA is low.
* The study will be submitted for publication to peer-reviewed journals regardless of whether the results favour or do not favour the study hypotheses.

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