Toxicon 119 (2016) 180–185

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Case report

Gonyautoxins: First evidence in pain management in total knee arthroplasty

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ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form
9 June 2016
Accepted 14 June 2016
Available online 15 June 2016

Keywords:
PSP toxins
Gonyautoxin
Pain management
Long-acting pain blocker
Periarticular infiltration

ABSTRACT

Improvements in pain management techniques in the last decade have had a major impact on the practice of total knee arthroplasty (TKA). Gonyautoxin are phycotoxins, whose molecular mechanism of action is a reversible block of the voltage-gated sodium channels at the axonal level, impeding nerve impulse propagation. This study was designed to evaluate the clinical efficacy of Gonyautoxin infiltration, as a long acting pain blocker in TKA. Fifteen patients received a total dose of 40 μg of Gonyautoxin during the TKA operation. Postoperatively, all patients were given a standard painkiller protocol: 100 mg of intravenous ketoprofen and 1000 mg of oral acetaminophen every 8 hours for 3 days. The Visual Analog Scale (VAS) pain score and range of motion were recorded 12, 36, and 60 hours post-surgery.

All patients reported pain of 2 or less on the VAS 12 and 36 hours post-surgery. Moreover, all scored were less than 4 at 60 hours post-surgery. All patients achieved full knee extension at all times. No side effects or adverse reactions to Gonyautoxin were detected in the follow-up period. The median hospital stay was 3 days.

For the first time, this study has shown the effect of blocking the neuronal transmission of pain by locally infiltrating Gonyautoxin during TKA. All patients successfully responded to the pain control. The Gonyautoxin infiltration was safe and effective, and patients experienced pain relief without the use of opioids.

1. Introduction

Adequate pain management has become a priority in health care, as declared by the Joint Commission on Accreditation of Healthcare Organizations (Badner et al., 1996). In surgery, a delicate balance is required between adequate pain relief and early mobilization. Pain after total knee arthroplasty (TKA) is associated with venous thromboembolism, coronary ischemia, pneumonia, insomnia, paralytic ileus, urinary retention, arthrofibrosis, and cognitive disturbance (Carr and Goudas, 1999; Kehlet and Holte, 2001; Ranawat et al., 2003; Singelyn et al., 1998; Maheshwari et al., 2009). In light of this, pain management plays a crucial role in recovery post-TKA (Rankin et al., 2004) and is usually patients' primary concern (Park et al., 2007; Lavernia et al., 2010). Successful pain management can cut the length of hospital stays, decrease opioid use (Wheeler et al., 2002), and reduce costs, as well increase range of motion (Shoji et al., 1990), enhance patient satisfaction, and reduce incidence of chronic pain (Ranawat et al., 2003; Singelyn et al., 1998; Maheshwari et al., 2009; Perkins and Kehlet, 2000; Chang and Cho, 2012). Nevertheless, studies have found that over 50% of patients suffer from undertreated pain (Parvizi et al., 2011).

There are many alternatives for pain management post-TKA, although there is no consensus as to which is the best option (Gibbs et al., 2012). The most frequently used are: epidural analgesia, epidural continuous infusion, intravenous patient controlled analgesia, and/or major nerve blockage or continuous intra-

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http://dx.doi.org/10.1016/j.toxicon.2016.06.010
0041-0101/

articular infusion (Davies et al., 2004), all of which have associated negative side effects. Nerve blockage is associated with paresis and risk of falls, which can delay rehabilitation (Capdevila et al., 2005), while the use of opioids has several side effects (Badner et al., 1996; Niemelainen et al., 2014). In addition, intra-articular infusions have recently been associated with chondrolysis (Ong et al., 2010). The Multimodal Pain Control (Parvizi et al., 2011; Ranawat et al., 2003; Ranawat and Ranawat, 2007), established in 1988 to improve control post-operative pain in total joint replacement, targets different pain pathways through peri- or intra-articular infiltration using local anesthetic (Ranawat and Ranawat, 2007; Noyes et al., 2012; Kerr and Kohan, 2008; Kelley et al., 2013), NSAIDs (Vendittoli et al., 2006) and/or corticosteroids (Fu et al., 2010), morphine (Ritter et al., 1999) antibiotics and epinephrine (Maheshwari et al., 2009), resulting in almost 48 hours of pain control, without the complications described above (Kehlet and Andersen, 2011).

In the last two decades, there has been great interest in using toxins from plants, animals, and microorganisms in physiology studies with animal models, to search for potential clinical applications. The most notable example is the clinical use of botulin toxin type A (Botox®), which has been proven beneficial in several therapeutic approaches (Jankovic and Brin, 1991). In recent years, research on the use of biotoxins from microalgae – primary producers that serve as the base of marine and fresh water food webs, and which produce secondary metabolic products with potent biological effects – has been growing (Lagos, 1998, 2014; Manríquez et al., 2015). Biotoxins are responsible for a wide array of human illnesses, with the Paralytic Shellfish Poisoning (PSP) posing the most serious threat to public health, due to its high mortality rate in mammals (Lagos, 1998, 2003).

PSP toxins, which are water-soluble, non-protein phycotoxins, consist over 25 structurally related imidazoline guanidinium derivatives, with a low molecular weight (Oshima, 1995). The high toxicity of PSP toxins is due to their reversible binding to a site receptor on voltage-gated sodium channels of excitable cells (Catterall, 1993; Golding, 2001), thereby blocking neuronal transmission (Strichartz et al., 1995; Catterall, 2000; Andrinolo et al., 1999, 2002; Lagos and Andrinolo, 2000). Specifically, PSP toxins bind with high affinity to site 1 of the alpha unit on voltage-dependent sodium channels (Na_V channel), inhibiting channel opening. These channels play a key role in neurotransmission at neuronal synapses and neuromuscular junctions. Consequently, the main physiological effect of PSP toxins is linked to their blocking action on the axonal level, impeding both nerve impulse propagation and neuronal transmission over the neuromuscular junction. Therefore, when applied locally, two clinical activities are manifested simultaneously: (i) control of pain (anesthetic activity) and (ii) control of muscle hyperactivity (relaxant effect). One of the known PSP imidazoline guanidinium derivatives is the Gonyautoxin, an analog of Saxitoxin, the most studied toxin of this group (Lagos, 1998).

In recent publications, local infiltration of Gonyautoxin has been shown to be safe and effective in several clinical applications (Lagos, 2014). This study was designed to evaluate the clinical efficacy of Gonyautoxin 2/3 as a long-acting pain blocker in the management of pain after TKA, in order to propose a safe and effective therapeutic alternative for TKA pain control.

2. Methods

The principles of the International Ethical Guidelines for Biomedical Research Involving Human Subjects and Declaration of Helsinki (WHO, 2002) were strictly followed in the design of this study, which was approved by the Ethics Committee of the University of Chile Clinical Hospital (Acta N°70, 2015HCUCH). The purpose of the study and potential associated risks were discussed with each participant before enrollment, and their written informed consent was obtained before surgery.

2.1. Patients

This study recruited patients who required TKA due to unresponsive knee pain, with radiological evidence of osteoarthritis (with a Kellgren and Lawrence score of 2 or more).

2.2. Exclusion criteria

Patients with a mental disability that prohibited their comprehension of the study, with a body mass index (BMI) greater than 35, and/or a major neurological deficit and narcotic dependency were excluded.

2.3. Recruitment

Patients were recruited between April and May 2015, at the moment of their pre-operative appointment. During their appointment, they were presented with information about the study, the surgery, and the Gonyautoxin injection protocol, and interested participants signed the informed consent. Twenty-two patients were assessed during the study enrollment period, with five declining to participant and two excluded due to their BMI. In total, fifteen patients entered the study.

2.4. Gonyautoxin dose

Each dose of Gonyautoxin includes 40 μg of Gonyautoxin diluted in 1.0 mL of Sodium Chloride 0.9%, with pH 6.2 and isosmotic. The preparation of Gonyautoxin has been described previously (Garrido et al., 2004; Garrido et al., 2005; Garrido et al., 2007; Lattes et al., 2009; Lagos, 2014).

2.5. Surgery procedure

Standard TKA technique was followed, with the addition of the periarticular injection of Gonyautoxin during cementation. The spinal anesthetic (2.5 cc 0.5% bupivacaine), a medial parapatellar approach with posterior-stabilized implants from Vanguard BIO-MET®, minus tourniquet and without wound drainage, was performed. Thirty, intraoperative, periarticular injections of a solution containing 40 μg of Gonyautoxin in 30 cc were performed through cementation in the posterior capsule and in the retinaculum and collateral ligaments (medial and lateral), while the cement was hardening. The quadriceps tendon and subcutaneous tissue were infiltrated just before closure. Each injection had 1 cc, for a total dosage of 30 cc (Fig. 1).

Postoperatively, each patient had given a standard pain management protocol, which consisted of 100 mg of intravenous ketoprofen and 1000 mg of oral acetaminophen, every 8 hours for 3 days. All patients received venous thromboembolism prophylaxis with compression stockings, early mobilization, and 5000 iu of dalteparine subcutaneously. Physical therapy started the day after surgery and consisted of standing, partial load walking with two canes and knee range of motion exercises, performed twice a day. Patients were discharged when they achieved going up and down one flight of stairs with cane support, had a self-report VAS pain score less than 4, and had completed six doses of Cephazolin, in line with the University of Chile Clinical Hospital protocol.