SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3147.

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Klinikai neurológiai kutatások

című program

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Development of Innovative minimally invasive interventional pain technology for whiplash-associated disorder

PhD thesis

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Budapest, 2025

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List of abbreviations

AA - Atlantoaxial

AO - Atlantooccipital

C-spine - Cervical Spine

CMBB - Cervical Medial Branch Block

CNA - Cryoneuroablation

DMX - Digital Motion X-ray

GAD - General Anxiety Disorder

GON - Greater Occipital Nerve

IOCM - Inferior Oblique Capitis Muscle

MRI - Magnetic Resonance Imaging

MSC - Mesenchymal Stem Cells

OA - Osteoarthritis

ORT - Opioid Risk Tool

P2G - Phenol, Dextrose, and Glycerin

PHQ - Patient Health Questionnaire

PICL - Percutaneous Implantation of Craniocervical Ligaments

PROMIS - Patient-Reported Outcomes Measurement Information System

PRP - Platelet Rich Plasma

RCT - Randomized Controlled Trial

ROM - Range of Motion

US - Ultrasound

UW - University of Washington

VAS - Visual Analog Scale

WAD -Whiplash Associated Disorder

1 Introduction

Treatment of whiplash associated disorders has been the author's interest for over 15 years. The various presentations of WAD (neck pain, headache, fatigue) require a thorough understanding of the pathophysiology, which allows selecting the ideal treatment for each case.

The current work is the synthesis of various minimally invasive treatment approaches to WAD that were assessed in retrospective and prospective data collection. The techniques developed and published by the author are detailed in the thesis.

1.1 Whiplash Associated Disorders (WAD)

The incidence of whiplash injury and WAD in the US is estimated to be at 4 per 1,000 individuals (1–5). Whiplash injury and WADs constitute the most prevalent injury that is related to motor vehicle accidents. Approximately 83% of individuals that are involved in motor vehicle collisions suffer from whiplash injuries and WADs. The overall financial burden associated with a whiplash injury is estimated to be $3.9 billion per annum in the USA. This includes sick leave, medical care, and disability. The overall economic burden exceeds more than $29 billion when the litigation costs are added.

1.2 Anatomy of the cervical spine and craniocervical junction

The cervical spine consists of 7 vertebrae, making up 2 motion segments, the lower cervical spine (C3-7) and the craniocervical junction (C0-2). The C1 and C2 vertebrae are more specialized than the rest of the cervical vertebrae. The C1 is ring shaped and has no vertebral body. C2 had a prominent vertebral body and the dens, that serves as a pivot for rotational moves of C1. Collectively the C0-2 is responsible for 50% of the cervical spine flexion and extension (C0-1) and rotation (C1-2) (6). The lower upper cervical spine, less specialized, allows for the remaining 50% of movements. The disc is fibrocartilage, that serves as a cushion between vertebrae. The inner nucleus pulposus supported by the outer fibrous annulus is responsible for resisting compression, while the annulus resists tension, shear and torsion (7). The facet joints and capsular ligaments guide the movement is the spine while also adding to the stability. In addition, multiple ligaments are responsible for the stability of the spine. The alar, apical, transverse ligaments and posterior atlantooccipital membrane support the C0-2, while the ligamentum flavum, anterior and posterior longitudinal ligament, inter and supraspinous ligaments prevent excessive flexion, extension of the cervical spine, therefore protecting the spinal cord and exiting nerve roots. The cervical spine is the most mobile of the entire spine, consequently highly reliant on ligaments, discs and muscles for controlling normal motion and still providing stability (8).

1.3 Clinical presentation of WAD

WADs, according to the Quebec Task Force, can be defined as soft tissue or bony injuries that arise from side or rear impact, particularly because of motor vehicle accidents or other trauma, based on the acceleration-deceleration phenomenon of transfer of energy to the neck. Whiplash has a wide range of clinical manifestations including neck stiffness, muscle spasm, paresthesia, neck pain, and arm pain dizziness, brain fog, numbness, tingling, GI symptoms, facial pain, lumbar pain. Individuals suffering from whiplash injury or WADs also tend to suffer from psychological distress and problems with their concentration and memory, anxiety, cognitive issues, tinnitus, fatigue, blurry vision. The constellation of these signs and symptoms is cumulatively termed WAD (1,9).

Acute whiplash may encompass rapid and severe onset of neck pain and neck stiffness following the initial injury, arm pain, acute hospital admission, and neurological deficit. However, symptoms often develop days or even 2-3 weeks after the MVA.

Chronic whiplash can be seen in 40% of the patients involved in vehicle accidents and is characterized by the persistence of WAD symptoms beyond three months. 2-4.5% of these patients suffer from permanent disability.

Studies have identified several markers that denote delayed recovery of patients suffering from chronic whiplash. These include older age of patients at the time of whiplash injury, lower educational achievement, lawyer involvement, pre-existing neck pain, female gender, pain in the lower back, and part-time employment. Patients suffering from chronic whiplash tend to experience mood disorders, depression, and anxiety with a greater prevalence compared to individuals who are suffering from chronic whiplash. Patients exhibiting any of the adverse indicators discussed above shall require intensive treatment along with a referral to specialists in WAD, physiotherapist, or a pain physician. Individuals who are suffering chronic whiplash and neck pain following a whiplash injury may develop central hypersensitivity, dorsal horn neuron sensitization. Patients then develop hyperalgesia in response to muscular and cutaneous stimuli. This occurs not only in the patient's the neck region but also in body sites away from the initial site of injury. This can be explained by the imbalance in the system of descending pain modulation along with the modification of the nociceptive signal from the deep neck tissues (10–13).

WADs can be classified into Grades 0-IV based on the presenting clinical signs and symptoms. Grade 0 corresponds to no physical signs and no complaints related to the neck. Grade I is associated with complaints of neck pain, tenderness, and stiffness only, however, there are no physical signs in these patients. Grade II corresponds to musculoskeletal signs and complaints of neck pain. The former include point tenderness and reduced range of motion (ROM). Grade III corresponds to the development of neurological signs and neck complaints. The former includes absent or decreased deep tendon reflexes, sensory deficits, and weakness. Grade IV corresponds to the complaint of neck pain along with dislocation or fracture of the neck (1,9).

Cervicogenic Headache and Occipital Neuralgia in Whiplash Injury

WAD often results in cervicalgia and cervicogenic headache. The culprit is typically the C2-3 and C5-6 facet injury, which directly causes neck pain, refers pain to the head and by leading to microinstability of the cervical spine, also results in secondary muscle spasm and myofascial pain (14–16). Occipital neuralgia is characterized by paroxysmal pain, stabbing, or shooting in nature, which occurs in the sensory distribution of specific nerves. These include the dermatomes corresponding to the lesser occipital nerve and the greater occipital nerve. These nerves originate from the C2 nerve roots, with communication to the branches of the C1 and C3 roots (Figure 1).

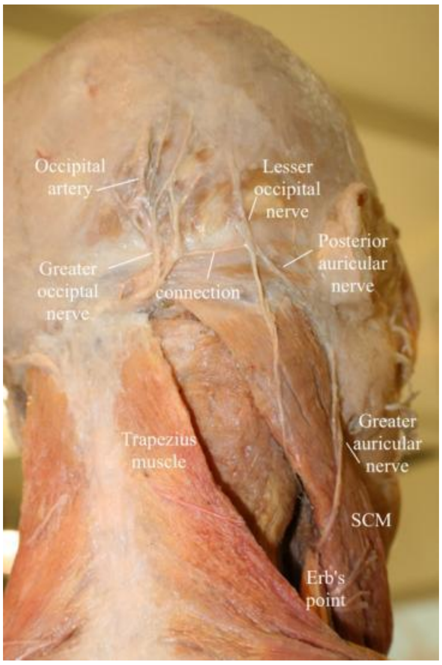

Figure 1. Dissection of the occipital region. A connection between the greater and lesser occipital nerve is visible. SCM, sternocleidomastoid muscle. Image courtesy of Andrea Trescot MD

The pain often starts from the suboccipital region, radiating towards the vertex. It also spreads to the upper neck, behind the eyes, and at the back of the head. Occipital neuralgia can also be associated with dysesthesia or hypesthesia involving the affected regions. The compression of greater or lesser occipital nerves constitutes the most common trigger for occipital neuralgia, with the former being more frequently involved. Sensitization of the

C1, C2, and C3 exiting nerves and dorsal root ganglions are also implicated in the development of cervicogenic headache, which is referred pain originating from cervical structures (17). There is a high prevalence of the development of acute post-traumatic headache following whiplash injury. Many patients who suffered from whiplash injury also report persistent headaches and neck pain. Based on the findings of a meta-analysis, there is a significant prevalence of headache and neck pain 12 months after suffering a whiplash injury. The entrapment of greater occipital nerve in whiplash injury gives rise to chronic occipital headache, which is along the distribution of the greater occipital nerve. (18)

1.4 Pathophysiology of WAD

Cervical ligament laxity may arise suddenly from a single macrotrauma, like a whiplash injury, or gradually from cumulative microtraumas, such as those caused by repetitive forward or bent head postures. In both scenarios, the cause of injury occurs through similar mechanisms, leading to ligament laxity and excess motion of the facet joints and cervical segments, which often results in cervical instability, also referred to as microinstability. Poor posture, genetic predisposition (Marfan's or Ehlers Danlos disease) or autoimmune diseases like rheumatoid arthritis can also lead to a similar clinical picture with cervical spinal microinstability.

The instability is characterized by the displacement of a certain cervical spinal segment to a greater-than-normal extent upon the application of force. Movement within the range of motion of an individual can elicit muscle spasms as well as pain in cases of cervical instability. The ligaments in the affected spinal segment, while performing a sensory function, elicit a ligament-muscular reflex. This causes the activation of muscles associated with this reflex, resulting in the preservation of joint stability. The activation of muscles can occur both directly and indirectly in muscles that do or do not cross the affected joint. With this, the sustained cervical spinal instability leads to a persistent increased muscle tone, muscle spasm, development of tight bands and eventually permanent myofascial pain from the overload and decreased circulation. The muscle spasm and later the further worsening of the biomechanics and spine alignment leads to nerve entrapment like occipital nerve entrapment, degeneration of the cervical spine and discs, sometimes leading to radicular compression and spinal stenosis on the long run. (Figure 2) (8).

Compared to joints with cervical instability, hypermobile joints demonstrate greater segmental mobility. However, hypermobile joints can sustain their normal stability and function when subjected to physiological loads.

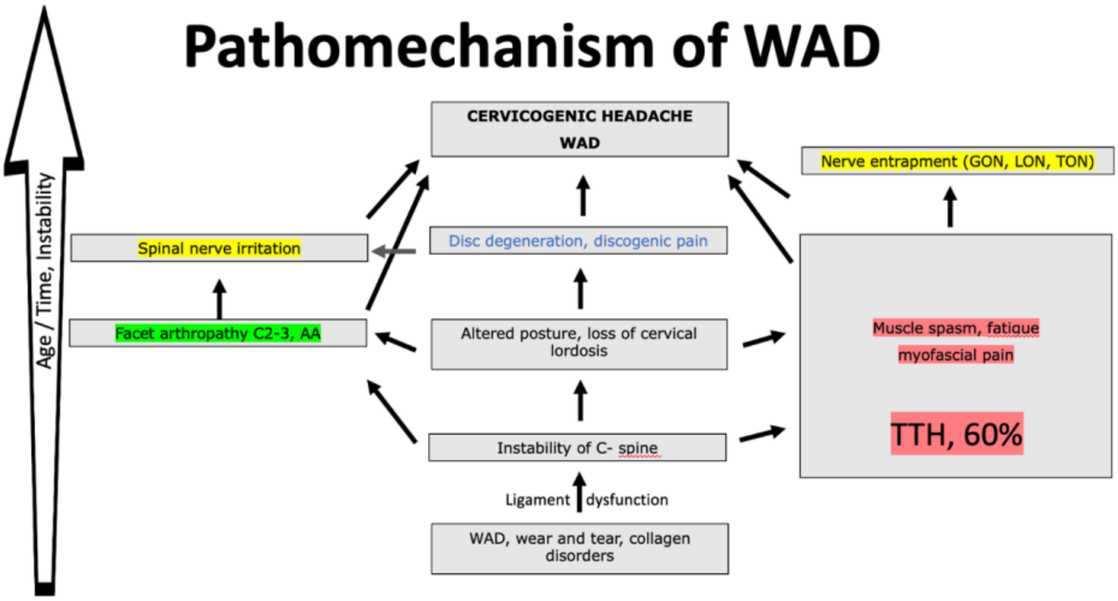

Figure 2. The proposed pathomechanism of whiplash associated disorders and cervicogenic headaches (TTH = Tension Type Headache, GON = Greater Occipital Nerve, LON = Lesser Occipital Nerve, TON = Third Occipital Nerve). Image courtesy of Agnes Stogicza MD

90% of the cases of whiplash injuries are associated with rear-end and low-impact collisions at the speed of < 14 mph. The trunk is forced in the backward direction on the seat, which is associated with the hyperextension of the neck, followed by a forward recoil. The risk factors associations with whiplash injury in motor vehicle collisions include female gender particularly women with thinner necks, car seats having a low neck-rest, individuals having a short neck, and when the rear-end collision occurs against a heavy vehicle. Car seats having an elastic back contribute to reduced risk of neck injury and subsequent neck pain following a car crash. According to research, 60% of the source of pain in whiplash injury originates from the zygapophysial fact joint, particularly at the C2-C3 and C5-C6 vertebrae levels instead of muscles in the neck region (12). T bone injury may put the C1-2 joint at higher risk because of the orientation of the joint itself.

1.5 Diagnosis of Whiplash Injury

The diagnosis of whiplash injury and WAD is mainly based on the presentation of the patient and the clinical findings observed in the examination of the patient (12,13).

Rapid acceleration or deceleration with excessive or sudden neck extension, rotation, or flexion is a key characteristic in patient history. The symptoms of whiplash injury can be delayed from hours to weeks following a motor vehicle accident or other trauma. The most common symptoms of whiplash injury in the affected patients include disabling unilateral or bilateral pain in the neck and headache, tight cervical musculature, foggy vision, difficulty concentrating, occipital neuralgia. The neck pain may or may not be referred to the back of the head, behind the eye or the arm or shoulder of the patient. Severe cases may present with dizziness, so called occasional “flash headache” that is the result of craniocervical junction instability temporarily impinging the exiting nerve roots.

Physical examination of the patient often shows decreased range of motion of the cervical spine, tenderness of the facet joints on palpation, muscle spasm, taught muscle bands, that may affect both the cervical musculature and the shoulder girdle. Greater occipital nerve entrapment results in tenderness at occipital nerves. Unilateral hypoglossal or other cranial nerve palsies, double vision, altered facial sensation, occasionally Horner’s syndrome, or torticollis may also be present and signal craniocervical instability. Features associated with serious spinal instability or other abnormalities should be considered. These include myelopathy or compression of the spinal cord, skeletal injury, vascular insufficiency, upper motor neuron signs.

Potential psychological barriers that may hinder recovery should also be identified. These include depression, stress, or anxiety. Whiplash injury and WAD are likely to occur in patients suffering from anxiety, depression, higher scores of somatization, obsessive compulsive disorder, and hypochondriasis.

The radiological investigations (MRI, X-ray) of patients in the acute stage of whiplash injury Grade I-III are typically unremarkable. However, 8% of the patients with normal cervical X-ray demonstrate instability on flexion-extension films (19) and an autopsy study found that only one out of 10 gross ligamentous disruptions was evident on X-ray (20). The most common radiological finding is loss of lordotic curve of the cervical spine. Flexion-extension X-ray or resting X-rays may show increased translation/displacement (>3.5 mm or 20%) or angulation (11%) according to White and Panjabi (21,22), however according to Knopp, the cutoff between normal and abnormal values is 2mm subluxation (23).

CT, flexion-extension CT, flexion-extension or regular MRI are an emerging techniques for similar measurements and for the assessment of the craniocervical junction(24). Instability may be identified by increased predental space (>3mm in adults, >5mm in children), basion-dental and basion-axis (>12mm) and increased Grabb Oakes (>9mm) measurements. All these measurements must always be correlated with the clinical findings, nevertheless. Dynamic Motion X-ray has been implicated as an additional tool in identifying cervical spinal instability, with similar measurements. DMX can also assess C1-C2 overhang (pathologic>3mm) in lateral flexion (25). To adequately depict instability in the cervical spine, functional imaging technology is essential, as opposed to static standard films. This technology allows dynamic imaging of the neck during movement, providing valuable insights for assessing the existence and extent of cervical instability. During the extension and flexion of the neck may also exhibit a kyphotic angle in the start. This may be due to ligament laxity of the posterior elements, decreased cervical spine mobility, caused by the imbalanced muscle function in the neck. This promotes increased mobility at the adjacent level of the spine.

These changes can often go unnoticed in a routine emergency setting if the patient does not report severe cervical pain and serious neurological symptoms.

1.6 Treatment Options for Whiplash-Associated Disorders

Whiplash injuries and WADs are challenging to treat for several reasons. Individuals who had suffered from whiplash injuries may present with complaints regarding paresthesia and pain. These complaints often lack clinical or radiologic evidence to confirm a whiplash injury. The variability in the effectiveness of treatment of WADs and whiplash injuries is also due to complex association between physical, psychosocial, and legal factors (1).

1.6.1 Conservative Measures for Relieving Pain in Whiplash-Associated Disorder

Conservative treatment measures constitute the most common options for relieving pain in patients who had suffered whiplash injury. Staying active, following an exercise regimen, simple analgesics and short course opioids have been shown to benefit patients with acute WAD (26). There is limited evidence to support the use of manual therapy, thoracic and cervical manipulation, Kinesio taping, but may be useful in individual cases. There is insufficient literature to show benefit or harm for other conservative methods, like Traction, Pilates, Feldenkrais, Alexander technique, massage, homeopathy, cervical pillows, magnetic necklaces, spray and stretch, heat, ice, transcutaneous electrical nerve stimulation (TENS), electrical stimulation, ultrasound, laser, shortwave diathermy (26,27).

1.6.2 Minimally Invasive Treatment Options for Whiplash-Associated Disorder

There are several surgical and minimally invasive interventions for the treatment of whiplash injuries and WAD. Sterile water intracutaneous injections have been used in small studies and shown benefit, however not routinely recommended. Studies assessing the use of Botulinum toxin A are conflicting. The use of corticosteroid intra-articularly and as selective nerve root blocks are useful for short term relief; however, they did not demonstrate any efficacy long term.

Radiofrequency ablation for Pain management

Radiofrequency neurotomy of the medial branches has been used and studied in various RCTs, with particular focus on the third occipital nerve, denervation of the C2-3 zygapophyseal joints. The relief provided by radiofrequency neurotomy is typically 8-12 months. The procedure may be repeated; however often with decreased success (15,28–30). Ultrasound (US) is increasingly used for cervical medial branch blocks (CMBB) due to benefits like soft tissue and needle visualization, accessibility, affordability, and safety. However, it has limitations, such as inadequate orientation, lower image quality in high body mass index (BMI) patients, and inability to assess injectate spread precisely. Fluoroscopy remains the gold standard, and US is an experimental modality for reimbursement by United States health insurers. The currently published and practiced US-guided cervical medial branch block methods that are taught by various anesthesia and pain societies have only been validated in a few cadaveric and clinical studies, mainly by 2 groups: the Finlayson group and the Eichenberger-Siegenthaler group (31–37). Clinical studies on efficacy are emerging, but the literature is still missing data on safety and efficacy. Cervical injections are high-risk procedures, and various devastating complications, including direct spinal cord injury, spinal cord compression due to hematoma, anterior spinal cord syndrome, brain stem, and cerebellum ischemia due to inadvertent vertebral artery compromise have been published (38–42). In 2017 an US-guided CMBB resulted in a spinal cord injury (43).

Dextrose and lidocaine intra-articular injections have been shown to provide sustained relief, however the quality of evidence is weak to establish the effectiveness of this treatment (44,45). Surgical options for severe WADs are available and often include fusion of the unstable segments. Reconstruction of the craniocervical junction is challenging, but crucial, as the consequences of an unstable CCJ are life-threatening (46,47). Occipital nerve decompression has also been implicated in the treatment of WAD, however results vary, and the procedure cannot be recommended routinely prior to further investigations(48). Detailed discussion of the surgical options is beyond the scope of this work.

Cryoanalgesia for Pain management

The utilization of cold temperatures to achieve analgesia has been implicated in medical practice for centuries. In cryoneurolysis, extremely cold temperatures are applied to reversibly ablate peripheral nerves via the induction of Wallerian degeneration at -70C. Cryoneurolysis probes pass a gas at high pressure to their tip within inner tube. As the gas passes through a small opening a rapid temperature decrease follows (Joules Thompson effect), the temperature of the tip of the probe decreases and an ice ball is formed. The exposed axon undergoes degeneration, but the endo-, peri- and epineurium remains intact. This allows regeneration of the nerve which returns to full function in about 6-12 months (49).

The procedure of cryoanalgesia is used in different intractable painful and persistent conditions, predominantly the conditions that are associated with a peripheral nerve, which is identified as the causative target location. The clinical indications of cryoanalgesia procedure are based on the peripheral nerve targets. These include iliohypogastric nerves, sacral nerve roots (S4-S5) in coccydynia, ilioinguinal nerves (herniorrhaphy pain, laparotomy, and nerve entrapment), lateral femoral cutaneous nerves in meralgia paresthetica, intercostal nerves (neuralgia mastectomy, rib fractures, and thoracotomy pain), and pudendal nerves (rectal pain and perianal pain). The procedure of cryoanalgesia is also implicated in the management of phantom limb pain, idiopathic neuralgia pain, neuroma, temporomandibular joint pain, and paroxysmal trigeminal neuralgia (50).

Orthobiologics in pain management

The American Academy of Orthopedic Surgery defines orthobiologics as the utilization of natural substances to accelerate the recovery of musculoskeletal injuries. These substances in higher concentrations than normal, derived from the body itself, are employed to enhance the healing of fractures, as well as injuries to muscles, tendons, and ligaments. Typically, these injections contain cells, scaffolding, and growth factors. The most frequently used orthobiologics for addressing musculoskeletal pain include PRP, prolotherapy, and MSCs (mesenchymal stem cells). MSCs are primarily composed of bone marrow aspirate concentrate (BMAC) and adipose signaling cells (ASCs).

Platelet-Rich Plasma

Platelet-Rich Plasma (PRP) entails the utilization of an autologous platelet concentrate obtained through centrifugation of whole blood, resulting in supraphysiologic platelet concentration while concurrently eliminating other cellular constituents. PRP is a natural source of signaling molecules, and upon activation of platelets in PRP, the P-granules are degranulated and release the GFs and cytokines that will modify the pericellular microenvironment. Some of the most important GFs released by platelets in PRP include vascular endothelial GF, fibroblast GF (FGF), platelet-de- rived GF, epidermal GF, hepatocyte GF, insulin-like GF 1, 2 (IGF-1, IGF-2), matrix metalloproteinases 2, 9, and interleukin 8 (51). The postulated therapeutic mechanism underlying PRP's efficacy revolves around its capacity to instigate endogenous reparative mechanisms, orchestrate inflammatory modulation, facilitate growth factor delivery, and attract and activate mesenchymal stem cells. These concerted actions contribute to the establishment of a milieu conducive to tissue healing and concomitant pain amelioration.

Empirical investigations conducted in vitro have showcased PRP's capacity to engender downregulation of pivotal inflammatory mediators, notably interleukin-6 (IL-6) and IL-8, thereby potentially mitigating hyperalgesic responses (52).

The effects of PRP have been extensively documented for a variety of tissue types, in a vast number of different settings. Despite the uncertainty of some of its intrinsic healing mechanism and administration protocol differences, the early evidence of PRP’s use for musculoskeletal-mediated pain conditions has been encouraging. In vitro and animals studies have demonstrated positive results in numerous types of tissue injuries that frequently plague patients including muscle (53), tendon (54), meniscus (55), ligament, cartilage, osteochondral surfaces, nerve, and intervertebral disks (52).

Prolotherapy

Prolotherapy can be defined as a non-surgical regenerative injection technique, which involves the administration of small quantities of a specific irritant solution to the entheses or degeneration tendon insertions, adjacent joint spaces, joints, and ligaments. Prolotherapy, although not a blood product, functions in a similar way to other orthobiologics, and therefore discussed and used in similar way.

Studies suggest that the stimulation of an inflammatory response results in a greater level of the cross-sectional area of the ligament following prolotherapy injection with a dextrose solution (56–59). The alleviation of joint degenerative disorders associated with the administration of prolotherapy injections can be explained by the creation of a hyperosmolar environment in the target site, which causes cell rupture followed by the release of platelet-derived growth factor (60).

This healing process is comparatively congruent to the natural healing process of the human body. This process comprises the initiation of a local inflammatory cascade, which promotes the secretion of growth factors by the inflammatory cells, and the deposition of collagen (61).

Although the exact proliferant used in prolotherapy often varies, all solutions, excluding chemotactic agents, have the universal effect of inciting local tissue irritation, which leads to an influx of inflammatory cells. Inflammation, being the first step in the wound-healing cascade, results in the end-product of fibroblast proliferation with the subsequent deposition of collagen. These three agents correspond to distinct prolotherapy categories: osmotic agents, irritants, and chemotactic agents. Irritants cause harm to cell membranes, while chemotactic agents are believed to directly initiate the inflammatory process. Osmotic agents create local tissue irritation, prompting the recruitment of inflammatory cells, which triggers the sequence of healing responses (52). Among these, dextrose has been extensively studied and is considered the preferred proliferant due to its water solubility and capacity for safe administration in various regions (62). Chemotactic agents are the final class and include the commonly used sodium morrhuate. This class is purported to be a direct chemotactic agent to inflammatory cells, which differs from the former classes that induce inflammation indirectly (52).

2 Objectives

This study aimed at describing and synthetizing various new minimally invasive treatment options developed and /or studied by the author for relieving pain and disfunction associated with whiplash injury in affected individuals.

Review retrospective data of utilization of prolotherapy for WAD and prospective data collection of PRP used to address WAD related instability, headache and neck pain, particularly for the craniocervical junction.

Describe new technique of cryoablation of the proximal greater occipital nerve.

Assess and compare the precision and safety of the commonly performed US-guided cervical medial branch injection techniques (as published by Finlayson and Eichenberger-Siegenthaler) using fresh cadavers.

Study Design: Retrospective data analysis, prospective data analysis, technical description and cadaveric study

3 Methods

To address the underlying pathophysiology, namely the biomechanical disfunction and instability of the craniocervical junction and cervicothoracic spine, the patient may undergo regenerative treatment, which often yield long term pain and functional improvement. In those cases where regenerative approach is not feasible or does not yield acceptable outcome, radiofrequency or cryodenervation of the painful structures is still available.

3.1 Regenerative medicine -prolotherapy

Retrospective data collection on cervical prolotherapy and illustrative case of cervical prolotherapy

At University of Washington prolotherapy was offered at the Center for Pain Relief for various conditions, including low back pain, cervicogenic headaches, cervical facet syndrome and WAD. Retrospective review was performed of 27 chronic headache and/or neck pain patients who have failed both conservative and standard interventional pain therapies and were looking for an alternative to pharmaceutical pain management. Patients who had at least 4 sessions of prolotherapy were included in the review. They received hyperosmolar proliferative injections in the cervical facet joint and accessory spinal ligaments as detailed below. Follow-up ranged from 4 to 14 months post injection. Outcomes were based on a 5-question questionnaire evaluating pain perception and functional improvement.

The below case is an illustrative case that demonstrated improved pain and functional outcome after WAD and was published as a case a report.

A 62-year-old female, who was treated at the Center for Pain Relief, University of Washington, USA, between May 2015 and February 2017. The Washington Headache Center referred the patient to the Center for Pain Relief owing to previous successes of prolotherapy procedures for the treatment of challenging cervicogenic headache patients. The relevant clinical history of the patient included a motor vehicle accident, that took place 14 months before the patient presented to the clinic. Following the accident, the patient experienced daily headaches, upper and lower back pain, cognitive issues, and neck and arm pain. Following the accident, the patient was taken to the emergency department due to nausea, difficulty with word finding, severe sharp pain in the head and left part of the neck, headache, and difficulty with sleep and concentration. There were no remarkable findings on the brain MRI and cervical x-rays. C-spine MRI demonstrated facet degenerative changes at multiple levels and decreased cervical lordosis. However, there was no foraminal or spinal cord compromise. After the discharge of the patient, she continued to experience pain, accompanied by short-term impairment of her memory and balance problems.

Before her initial visit to the hospital, the patient had received substantial amount of diagnostic work-up and treatment from five primary care physicians, physical therapist, complementary medicine specialist, two pain specialists, psychologist, and three internists. The patient was refractory to a wide array of treatments including medications (non-steroidal anti-inflammatory drugs, paracetamol, nortriptyline, amitriptyline, gabapentin, pregabalin and oxycodone), behavioral therapy, chiropractic manipulation, ongoing physical therapy, intramuscular stimulation, trigger point injections, greater occipital nerve blocks with steroids, repeated C3, C4, and C5 medial branch block and third occipital nerve blocks.

Initial evaluation with standard self-report questionnaires included the following instruments (baseline scores revealed moderate disease severity): pain (visual analog scale, [VAS], 0–10 points); pain interference (VAS, 0–10 points); disability (Oswestry Disability Index, 0–100%) (63); depression (Patient Health Questionnaire, PHQ-9, 0–27 points) (64); anxiety (General Anxiety Disorder 7-item, GAD-7, 0–21 points) (65)(66); sleep initiation difficulty (VAS, 0–10 points); sleep maintenance difficulty (VAS, 0–10 points); and quality of life (Promise Global 10, 1–10 points). The patient had an Opioid Risk Tool (ORT-26) score of 10 (66), indicating high risk for opioid abuse. We used the online tool PainTracker to collect baseline and follow-up data at the point of care. (67).

Physical exam of the C-spine exam demonstrated forward head carriage without muscle atrophy, decreased cervical lordosis and decreased range of motion (ROM) in all directions (flexion: 35◦, extension: 45◦, rotation left: 30◦, rotation right: 35◦), limited by pain and tightness, with extension better tolerated than flexion and rotation. Tenderness on palpation was observed in her paraspinal muscles, splenius, sternocleidomastoid, trapezius, levator scapulae, supraspinatus muscles, the supra- and interspinous ligaments from the occiput to T4 and at C2-3, C3-4 and C4-5 facet joints bilaterally. Tenderness was also noted on palpation of the greater occipital, supraorbital and infraorbital nerves. The rest of the neurological exam was negative. The initial diagnoses were WAD, cervicalgia, cervicogenic headache, cervical ligament laxity, decreased cervical lordosis and multilevel cervical facet arthropathy superimposed with muscle spasm and myofascial pain secondary to flexion-extension injury.

The initial diagnoses were whiplash associated disorder, cervicalgia, cervicogenic headache, cervical ligament laxity, decreased cervical lordosis and multilevel cervical facet arthropathy superimposed with muscle spasm and myofascial pain secondary to flexion-extension injury. Conventional treatment approaches were ineffective; therefore, we developed the following treatment plan: 3–5 sessions of P2G prolotherapy (phenol, dextrose and glycerin) to be applied to the affected facet joints and ligaments with concurrent physical therapy. This was our routine approach to trauma, overuse and postural changes leading to neck pain and headache, where ligamentous laxity could be assumed as an underlying pathomechanism. Phenol, dextrose and glycerin are not labeled for ligamentous injection, but have been used by prolotherapists since at least 1990, without any reports on side effects or complications (68).

Treatment

The patient received prolotherapy with ongoing physical therapy while stopping all other treatments during the prolotherapy and follow-up period. Injection points were based on the C-spine treatment recommended in a standard prolotherapy textbook (69), and supplemented with the upper two joint capsules based on the severely limited ROM at rotation (C1-2) and flexion (C0-C1). The atlantooccipital (C0-C1) and atlantoaxial (C1-C2) joints have been shown to be symptomatic in individuals both with chronic whiplash-associated disorder and idiopathic neck pain (16,70,71). The injection of 0.5 ml of solution (dextrose 20%, phenol 0.5%, glycerin 10%, lidocaine 0.5% in normal saline) (68) was applied at each site every 2 weeks for four sessions. The following sites were injected using fluoroscopic guidance: bilateral AO joints (Figure 3) and AA joints (Figure 4), cervical and thoracic facet capsule joints (Figure 5) at each level from C2-T4 with a posterior to anterior approach and supraspinous ligaments. The superficial cervical muscle attachments (trapezius, semispinalis capitis, splenius capitis and sternocleidomastoid muscle) and deep cervical muscle attachments (rectus capitis posterior major and minor, and obliquus capitis superior) at the occiput and the sternoclavicular joints were injected using a palpation and landmark-guided technique (Figure 6).

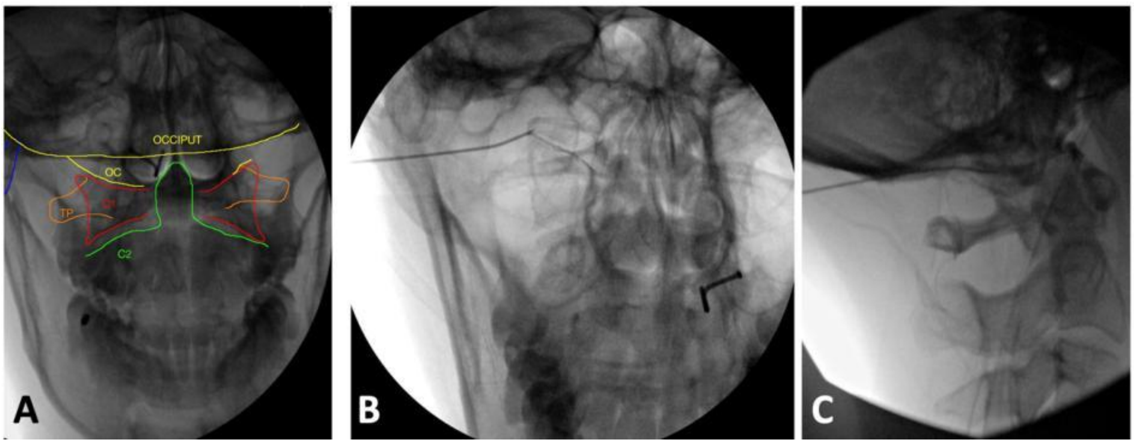

Figure 3. Fluoroscopy-guided atlantooccipital joint injection. AP fluoroscopy view, marked image (A), needle in the right atlantooccipital joint, contrast outlines the joint space (B) and lateral image (C). Yellow = occiput and condyle, Red = C1 vertebral body,

Orange = C1 transverse prcocess; Green = C2 vertebra. Image courtesy of Agnes Stogicza MD.

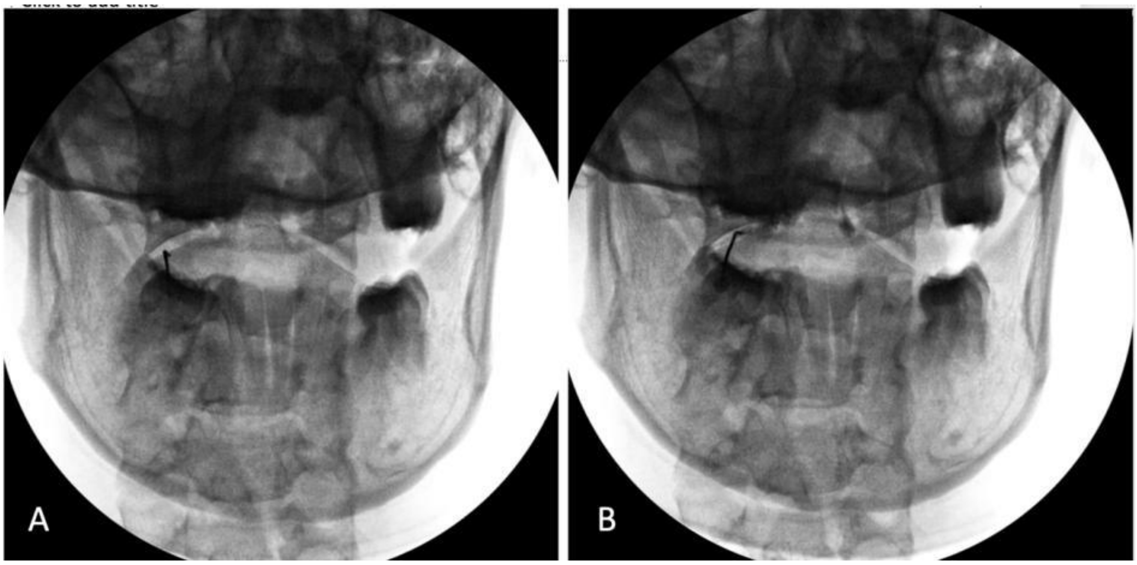

Figure 4. AP fluoroscopy image of atlantoaxial joint injection. A 22G 100mm curved Quincke needle is driven to the lateral third of the AA joint, touching on the upper rim of the lower facet (A). After bony contact is encountered, the needle is rotated cephalad and guided into the joint. 0.2ml contrast confirms intraarticular position (B). Image courtesy of Agnes Stogicza MD.

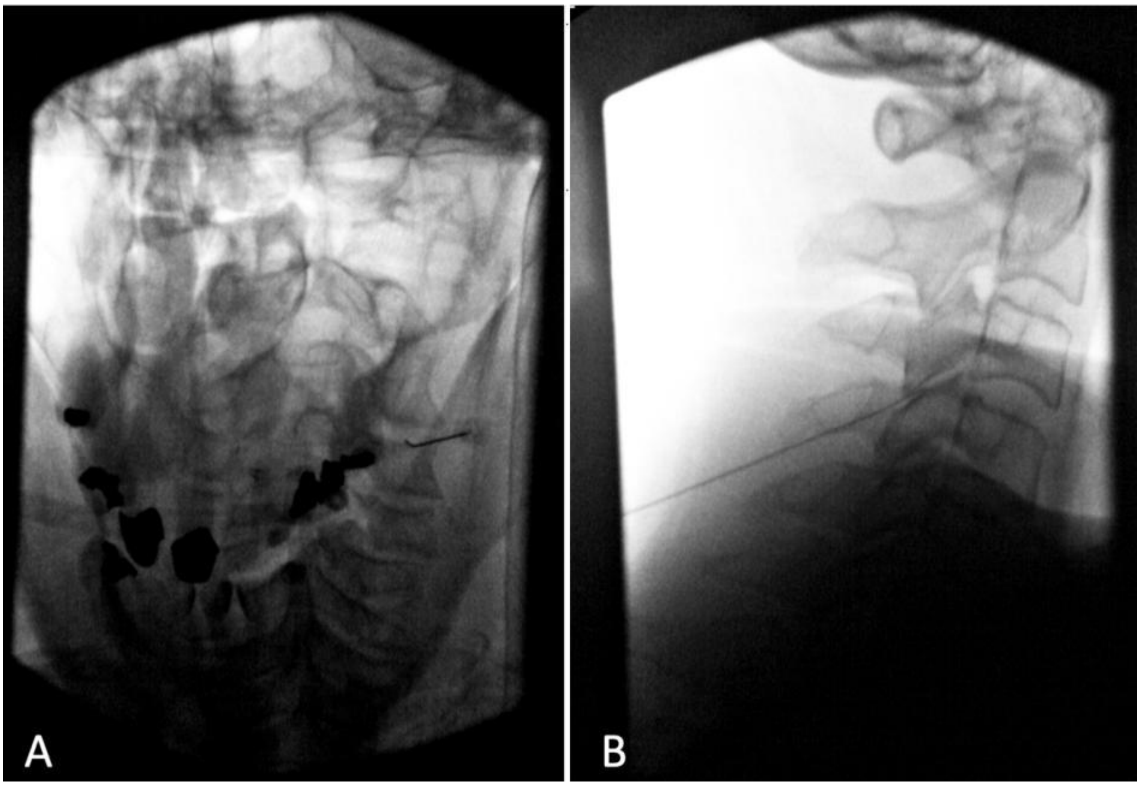

Figure 5. AP (A) and lateral (B) fluoroscopy image of the C3-4 facet joint injection. Image courtesy of Agnes Stogicza MD.

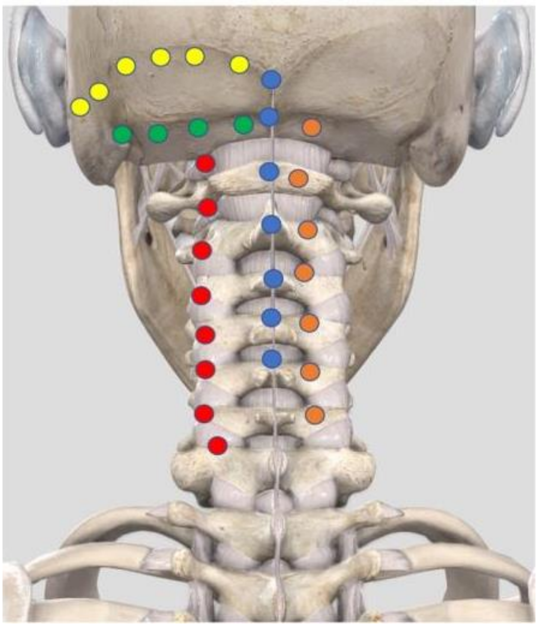

Figure 6. Treatment targets for regenerative medicine. Blue = Spinous process, Red = facet joint, Orange = lamina, Green and Yellow = deep and superficial cervial musculature attachment. Image courtesy of Agnes Stogicza MD.

3.2 Regenerative medicine - PRP

Prospective case series on cervical PRP treatment and an illustrative case of cervical PRP treatment with PICL procedure

Cervical PRP treatment is based on a similar concept to prolotherapy, but while prolotherapy initiates the inflammatory cascade via cell injury and lipid leakage, PRP may trigger it by direct platelet injection and activation.

The author has performed cervical PRP treatment since 2006, however data collection was only available since 2018. Between 2018 and 2024 a total of 502 PRP treatments were performed at the PSI Pain Clinic/Saint Magdolna Private Hospital of which 56 were cervical PRP procedures, in order to decrease cervicogenic headache, cervicalgia. 7 patients treated for identifiable trauma induced WAD between 2020 and 2024 have been evaluated and followed for over 3-25 (average: 18months follow up). Neck disability Index was used to track functional outcome and VAS to track pain levels at 0, 6, 12, 18, 24 and 36 months. (Table 1.)

The patients underwent PRP treatment of the cervical spine and the craniocervical junction (PICL procedure). The injection targets were identical to the prolotherapy patient #1 (Figure 6) but were supplemented with transoral injection to the median atlantoaxial joint, alar and apical and transverse ligaments twice, 3 months apart. The PRP was prepared with the double spin EmCyte PRP system, which yields a red blood cell free, leukocyte poor platelet product, with 6-8x of the baseline platelet count.

The below case is an illustrative case that demonstrated improved pain and functional outcome after WAD.

33-year-old previously healthy female was rear ended in with approx. 70-80km/h. 24 hours after injury she developed neck pain and headache. After slow recovery patient returned to her normal functions as full-time manager of a woodchip company and mother of two. 2 years later she suffered a second, low speed rare end collision. Neither accident resulted in loss of consciousness. Severe symptoms developed 3 hours after the accident: brain fog, tremor of the hands, drop attacks, blurred vision, nausea, tingling of hands and toes, dizziness, tremor, increased heart rate, cold, dysphagia, photophobia, headaches. Physical exam showed tenderness of the C-spine, torticollis. Supine position decreased her symptoms. Multiple ER and two independent neurosurgical consults suggested that the symptoms were psychosocial. The recommended lifestyle adjustments and psychotherapy lead to no results. 3 years after the last accident the patient was unemployed, unable to care for herself and family.

Physical exam showed decreased ROM of the cervical spine in all directions, with extension being particularly painful, and provoking dizziness. Cervical facets and cervical musculature bilateral GON were tender to palpation, with exquisite tenderness to pressure over the C2 spinous process. Spurling test and neurology exam were negative. Cervical MRI demonstrated slight kyphotic change at C3-4-5 levels, but no other major changes. Digital Motion X-ray was performed in USA Florida and demonstrated cervical spinal instability. 2.7mm retrolisthesis of C2 on C3 in extension (Figure 7), 2.4mm and 1.9mm anterolisthesis of C3 on C4 and C4 on C5 respectively in flexion (Figure 8). Gapping of the facet joints at C5-C6 on the right and C6-C7 was obvious bilaterally on oblique flexion (Figure 9) and significant abnormal lateral translation of C1 on C2 with 4.8mm overhang bilaterally on lateral flexion. (Figure 10) Neck Disability Index value was 36/50 (75%).

Table 1. Demographic, symptoms, clinical findings and previous treatments. Demographic data was displayed with age/gender/body mass index. MVA = motor vehicle accident, BPV = Benign Paroxysmal Vertigo, ROM = range of motion, PT = Physical therapy

Demographic	Cervical MRI and physical exam	Subjective	Previous treatments
BE 46/F/29	C-MRI: Decreased cervical lordosis. Tenderness to palpation upper cervical facets, decreased right rotation and right flexion	Previous neck injury followed by BPV treated with Epley maneuver. Sudden start of symptoms: Headaches, neck pain, inability to work	Medication management PT Steroid inj. x 13
SJ 35/F/24	C MRI: Decreased cervical lordosis Overall decreased ROM of C spine. Head movements result in dizziness. Tenderness to palpation upper cervical facets, and supraspinous ligaments, splenius and semispinalis attachments	Trauma (caught child with sled, to prevent sliding to traffic). Further complicated by cervical manipulation. Inability to work, care for self and family. Leading symptom: dizziness, inability to walk without cane, cervicalgia	Medication management Psychotherapy, PT Paravertebral steroid inj. x3, with initially good relief Cervical manipulation
LK 41/M/26	C-MRI: Mild degenerative changes decreased lordosis. Severely decreased cervical ROM, neck movement leading to nausea, dizziness. Palpation tenderness at facets and supraspinous ligaments.	English teacher with multiple snowboard accidents. Barely maintains work, unable to care for young child. Inability to bend forward lay supine, turn from neck, to work b/of headaches and dizziness, instability of spine, supine position led to nausea.	Medication management PT, steroid infusion x2
RB 33/F/23	C-MRI: Mild degenerative changes decreased lordosis. DMX: C1-2 4.8mm overhang C2-3 2.7mm retrolisthesis C3-4 2.4mm anterolisthesis Palpation tenderness of the C-spine, torticollis	MVA x2, inability to work, care for self and family.	Medication management PT, lifestyle modifications, psychotherapy Steroid inj.

PM 38/M/22	C-MRI: No degenerative changes. DMX: C1-2 4mm overhang C2 2 mm anterolisthesis C3 4 mm anterolisthesis C6 5mm anterolisthesis Palpation tenderness of the C-spine, GON, supra, infraorbital nerves, myofascial tenderness, pressure over C2 spinous process provokes dizziness,	High functioning IT worker with major bicycle C-spine injury. Inability to work and care for self, constant dizziness, visual disturbances, neck pain, occipital neuralgia.	Medication management PT, lifestyle modifications, psychotherapy Steroid inj.
KK 29/M/21	Kinetic-positional C-MRI: decreased lordosis, right-convex torsional scoliosis with apex in the C5/6 segment and 18 degrees scoliosis angle and angular instability: paradoxical kyphosis C5/6 DMX: dens obliquity with displacement to the left in neutral position. C1-2 4 mm overhang in lateral flexion,	Previously healthy male with MVA approximately 2 years prior. No LOC. Since then, persistent, predominantly posture-dependent pain, "head pressure", brain fog, blurry vision, imbalance, dizziness, TMJ tenderness, muscular tension. On disability.	Medication management PT, lifestyle modifications, psychotherapy Prolotherapy at AA joints x1
SzD 50/F/25	DMX: dens obliquity with displacement to the left in neutral position. Left C1-2 4,2 mm overhang in lateral flexion, C2-3 2mm anterolisthesis in flexion, C3-4 1,6mm, C4-5 1,6mm, C5-6 3,1mm anterolisthesis in extension	More than 10 years of pain radiating to the right shoulder, head, arm, face, and sometimes to the chest, arm. Chronic fatigue syndrome. Multiple childhood concussions and a fall from a height landing on her chin.	Medication management PT

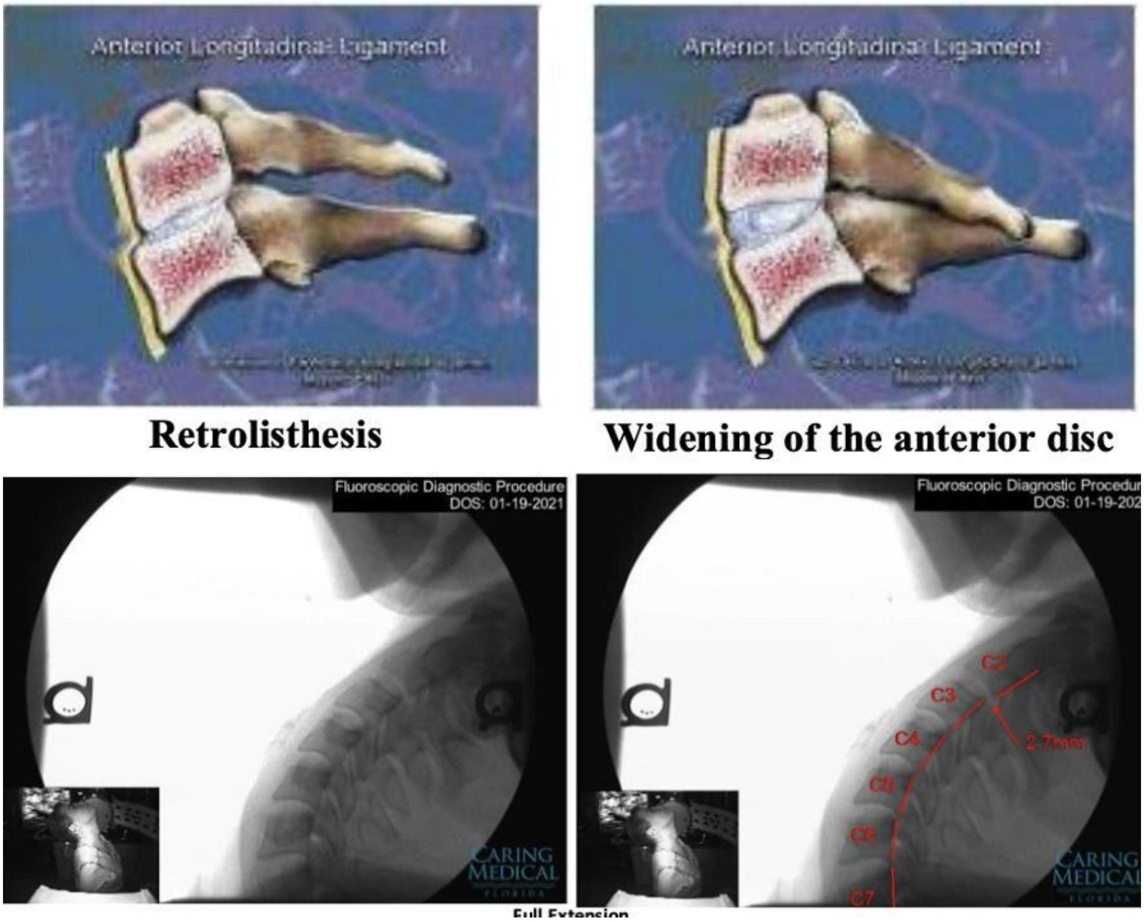

Figure 7. Digital Motion X-ray was performed and demonstrated cervical spinal instability. 2.7mm retrolisthesis of C2 on C3 in extension. This view examines the integrity of the anterior longitudinal ligament demonstrated by a backward (posterior) movement of one vertebra over the vertebra below or by the anterior widening of the intervertebral disc space (increased disc angle). Image courtesy of Agnes Stogicza, used with permission of the patient, RB.

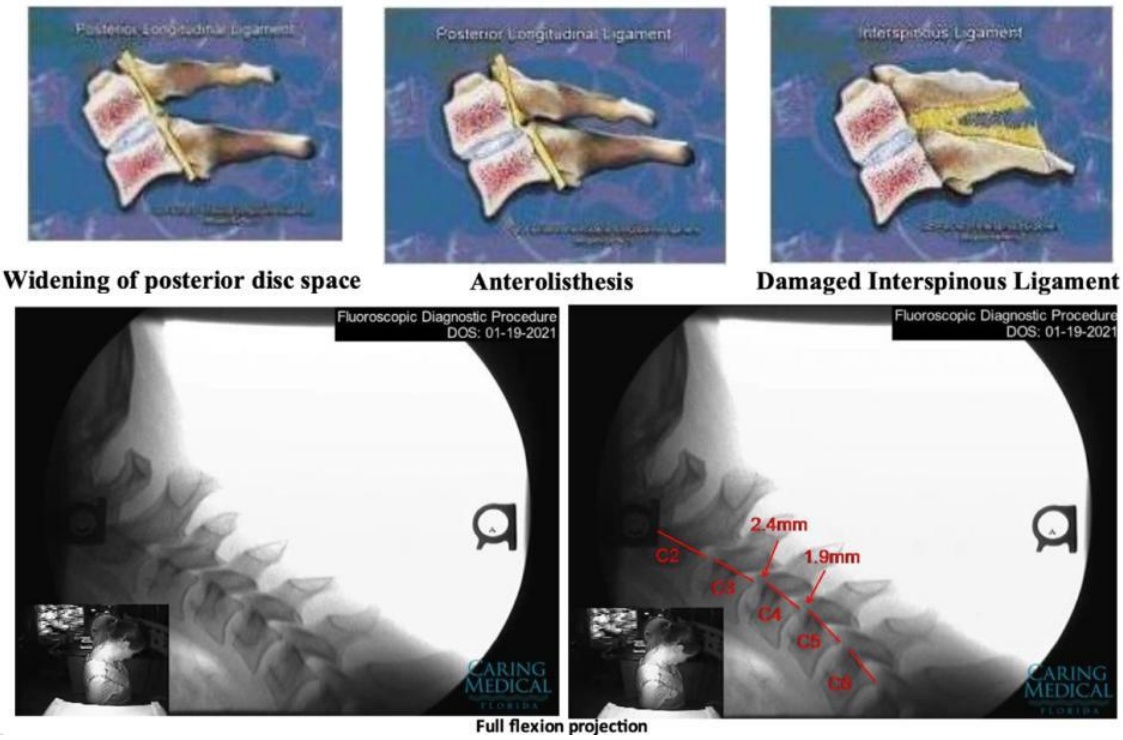

Figure 8. Digital Motion X-ray was performed and demonstrated cervical spinal instability. 2.4mm and 1.9mm anterolisthesis of C3 on C4 and C4 on C5 respectively in flexion. This view examines the integrity of the posterior longitudinal ligament demonstrated by a forward (anterior) movement of one vertebra over the vertebra below or by the posterior widening of the intervertebral disc space (increased disc angle). Image courtesy of Agnes Stogicza, used with permission of the patient, RB.

Figure 9. Digital Motion X-ray. Gapping of the facet joints at C5-C6 on the right and C6-C7 was obvious bilaterally on oblique flexion. This view demonstrates facet capsular ligament damage. Image courtesy of Agnes Stogicza, used with permission of the patient, RB.

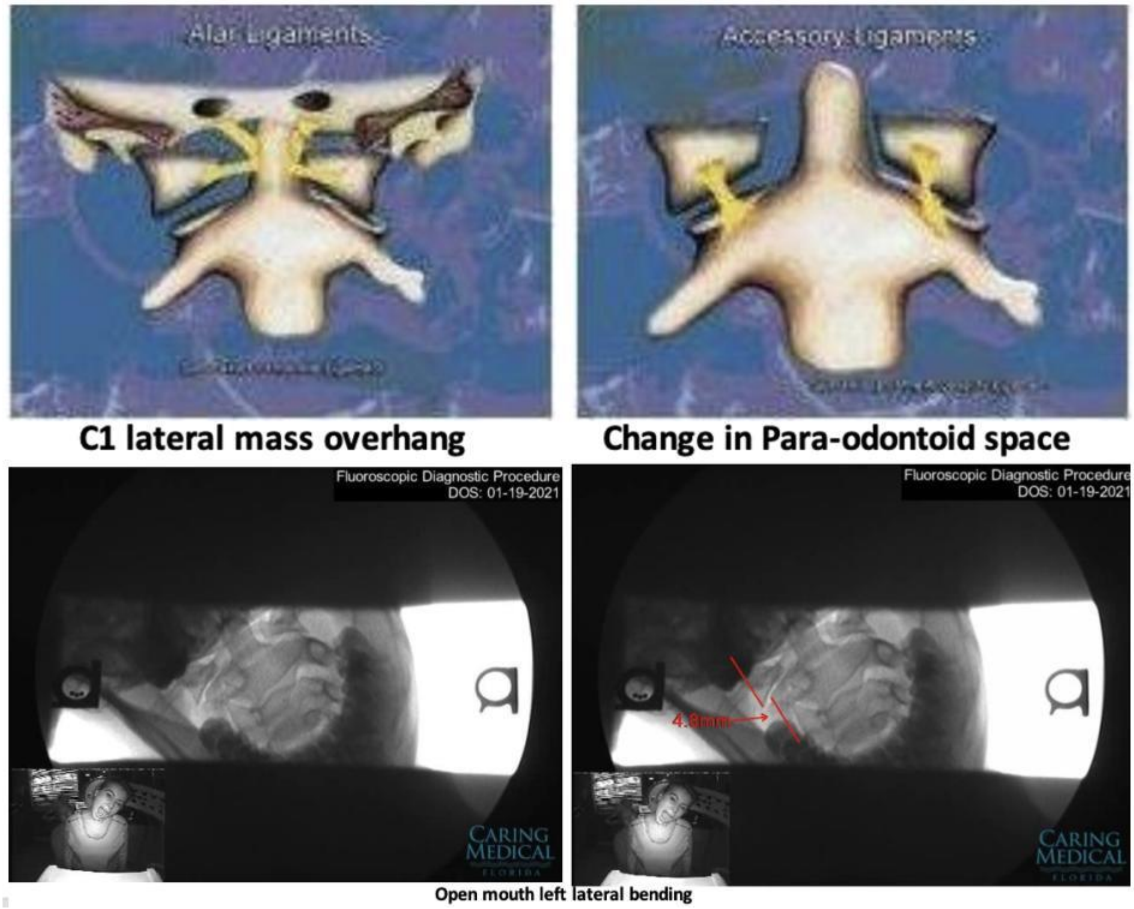

Figure 10. Digital Motion X-ray: significant abnormal lateral translation of C1 on C2 with 4.8mm overhang bilaterally on lateral flexion. This view examines the integrity of the alar and accessory ligaments either by the lateral overhang of C1 on C2 or by the changes in the para-odontoid spaces. Image courtesy of Agnes Stogicza, used with permission of the patient, RB.

Treatment

All 7 patients underwent PRP treatment of the cervical spine two or three times. The initial targets were identical to patient #1 (Figure 6), but to further enhance recovery, supplemented with transoral access to the median atlantoaxial joint, alar, apical and transverse ligaments (Figure 11. A-C). The injections were performed 3 months apart. All patients included in our report provided written consent for this report. According to our institution ethic board, no ethic approval was required for this data review.

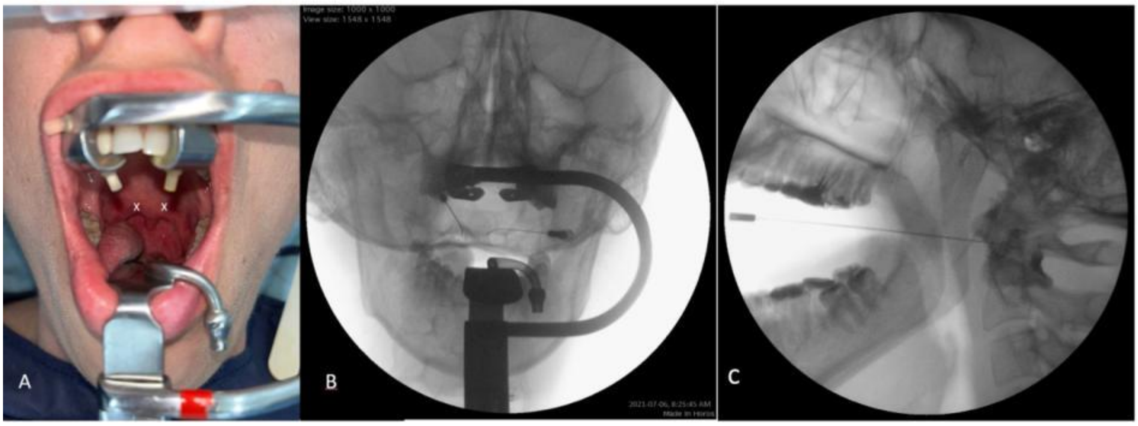

Figure 11. Fluoroscopy guided anterior Atlanto-Axial (C1-C2) PRP injection. Transoral access (A) to the median atlantoaxial joint, alar and apical and transverse ligaments, AP (B) and lateral view (C). X marks the entry points on either side of the uvula. Image courtesy of Agnes Stogicza MD.

In the cervicogenic headache, cervicalgia and WAD cases where either the clinical picture was strongly dominated by greater occipital nerve entrapment, or the patient refused regenerative medicinal intervention, cryoablation of the Greater Occipital Nerve (GON) was performed. The technique was described and published by the author.

3.3 Novel, Proximal Greater Occipital Nerve Cryoablation

Retrospective data analysis of the newly described procedure to assess safety

50 patients underwent cryoablation of the greater occipital nerve, according to the technique below. The procedures were performed at the University of Washington, during 2010 and 2016, by the author. The author continued to administer cryoablation in Hungary using this technique and reported similar outcomes without any complications in a further 6 cases of occipital neuralgia. The data was pulled from the UW patient database, and the procedure was assessed for safety.

Prior to cryoneuroablation the diagnosis is confirmed with a diagnostic injection, where a minimum of 80% pain relief is expected in the local anesthetic phase. It is crucial that the diagnostic block is performed with minimal volume (0.5-1ml) local anesthetic, in order to preserve specificity. It also serves as a predictive block, giving the patient an opportunity to briefly experience the outcome of cryoablation, both the pain relief and the numbness. Once the diagnosis is confirmed with the diagnostic block, cryoablation may be performed, usually on a different occasion.

The patient is required to lie in a prone position with the maximum flexion of neck as comfortably possible for the patient (Figure 12). Usually, a linear probe is used for the visualization of the GON. The ultrasound probe is placed over the spinous process of the second cervical spine in a horizontal manner, then the probe is slightly rotated and moved towards the C1 transverse process. This allows visualization of the inferior oblique capitis muscle, with the GON running over it at the junction of the medial one third and lateral two thirds. The diagnostic injection requires a 25-gauge needle, 2% lidocaine, and it is performed under the guidance of ultrasonography utilizing an out-of-plane approach (Figure 12).

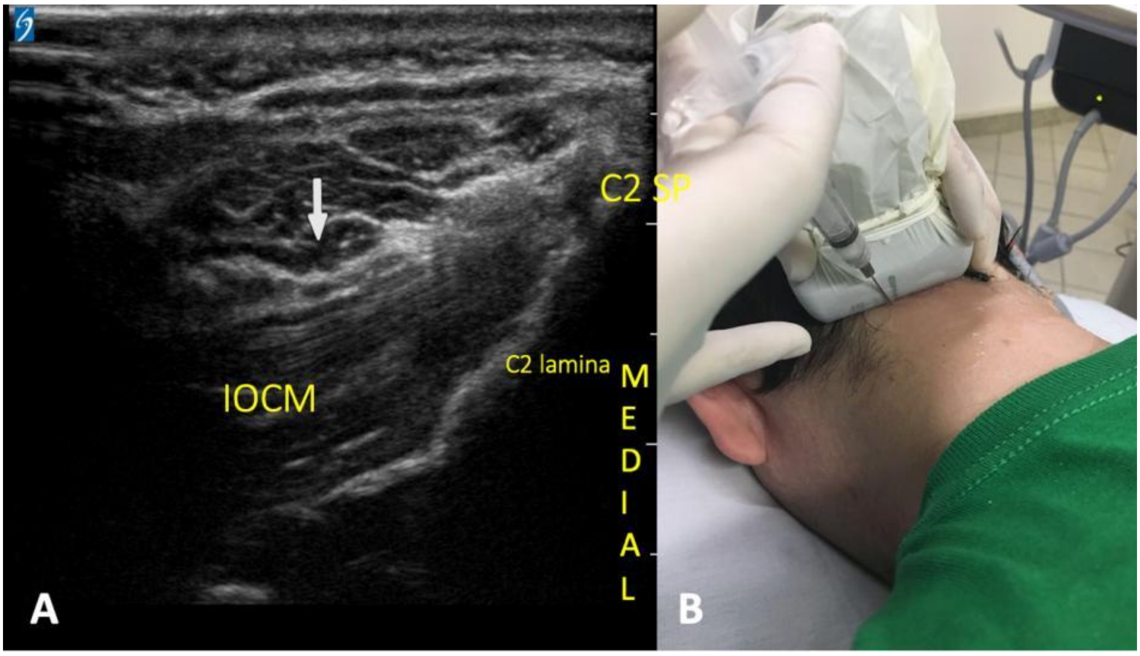

Figure 12. The diagnostic injection in a prone position, neck flexed in a head gel ring (B). It requires a 25-gauge needle, 2% lidocaine, and it is performed under ultrasonography guidance utilizing an out-of-plane approach. Arrow points at the GON, just posterior to the IOCM = inferior oblique capitis muscle, SP = spinous process. Image courtesy of Agnes Stogicza MD.

If the diagnostic injection was temporarily successful, the patient was then scheduled for cryoneuroablation of the affected nerves. Moderate sedation is often used to decrease patient discomfort; however, it is advised that the patient be awake and cooperating throughout the whole procedure to increase procedural safety. Our patients signed consents prior to treatment. Institutional review board approval was not sought, as patient care met the Declaration of Helsinki guidelines, in particular section 32, which pertains to new therapeutic measures and the recording of new information. We used the Wallach WA1000B Cryosurgical System (Epimed International, Dallas, TX, USA) which utilizes compressed N2O and trocar-tipped 14-gauge cryo probes in the USA and the METRUM Cryosurgical System (METRUM Cryoflex, Warsaw, Poland) with 1.3 mm wide 10 mm active tip in Hungary.

Cryoneuroablation of GON Procedure Description

Patient positioning and nerve identification occur as described above. After sterile preparation and draping, 2 to 3 mL of local anesthetic is infiltrated in the midline cutaneous and subcutaneous tissues at the planned cryo probe entry point and in the direction of the GON via a 27- or 30-gauge needle. After a small, 2-mm skin

incision is created, a 12-gauge IV catheter is used as an introducer and is placed through the subcutaneous tissues, the trapezius muscles, and the semispinalis capitis muscles, towards the GON. The catheter tip is placed close to the occipital nerve on the surface of the IOCM and the stylet removed. The cryo probe is then advanced through the catheter (Figure 13.A) and advanced to the GON under US guidance. Even without any electric stimulation, the patient often confirms that the placement of the probe provoked a paresthesia at the back of the head. Sensory stimulation (50 Hz) at progressively lower voltage (from 1 Volt to 0.3 Volt) can aid to accurately position the probe directly on the nerve if visualization is not sufficiently clear. Three 2-minute cryoneuroablation cycles are then performed at -70°C. The ice-ball appears as a hyperechoic round structure at the tip of the cryo probe and prevents the echo from spreading beyond the probe (Figure 13.B). As described above, the nerve can be tracked by US back and forth in a cephalo-caudad direction, which allows confirmation that the ice-ball has incorporated the GON, by visualizing the "nerve–ice ball–nerve" sequence. The vertebral artery is in the

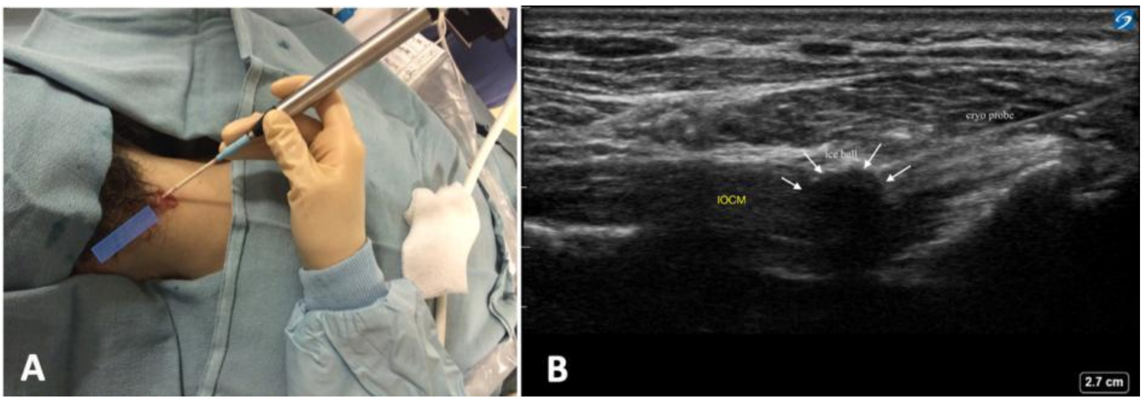

Figure 13. Cryoablation of the GON. The cryo probe is advanced through the catheter (A) and advanced to the GON under US guidance. The ice-ball appears as a hyperechoic round structure at the tip of the cryo probe and prevents the echo from spreading beyond the ice (B). Image courtesy of Agnes Stogicza MD.

trajectory of the needle; however, the artery is beneath the IOCM, far lateral to our target, and usually well visualized by 2- dimensional and color Doppler mode, so it can be easily avoided if US is used appropriately to identify anatomy (Figure 14). In patients with lower body mass index, it is also easy to visualize the spinal cord just beneath the IOCM, which again is helpful to understand risks and avoid them (Figure 15). Utilizing a medial to lateral in-plane approach allows for using an in-plane approach with the cryo probe pointing from medial to lateral, which keeps the spinal cord safe, away from the needle trajectory.

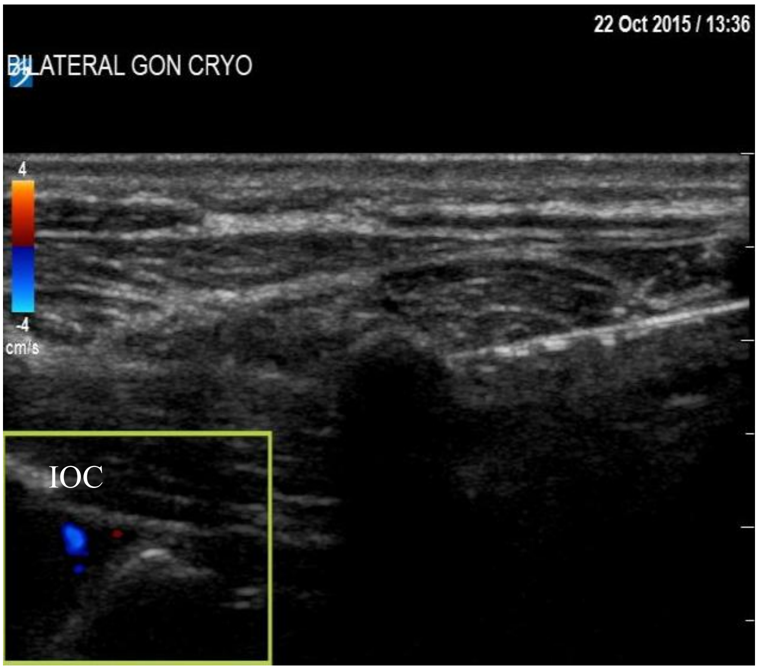

Figure 14. The vertebral artery is in the trajectory of the needle; however, the artery is beneath the IOCM, far lateral to our target, and usually well visualized by 2- dimensional and color Doppler mode. Image courtesy of Agnes Stogicza MD.

Figure 15. Spinal cord visible just beneath the IOCM between C1 and C2. Yellow arrow = spinal cord, white arrow = dentate ligament

In advanced long-standing cases of instability of the cervicothoracic, scapulohumeral region, an accelerated degeneration of the shoulder joint is often observed, as detailed above. These patients have few options to increase function. Shoulder arthroscopy and replacement leads to varying outcomes and are only suitable in selected cases, and even then, it requires a prolonged time to recovery. These patients may benefit from cryodenervation of the shoulder joint. The below, motor sparing approach to shoulder denervation is new, described, published by the author.

3.4 CMBB injection comparison of two techniques

3.4.1 Cadavers

After obtaining approval from the Institutional Review Board of Semmelweis University, we included 3 male and 2 female fresh, full, undissected cadavers selected randomly. Their ages ranged from 42 to 72 years old, with a mean age of 67. Their BMI ranged from 19 to 26, with a mean of 23.2. Three of the cadaver necks were deemed arthritic by the sonographers. A Sonosite Edge 2® Ultrasound System (Fujifilm Ltd) with a 13-6-MHz high-resolution linear transducer and BRAUN 20G 50mm echogenic needles were used.

3.4.2 Study Participants

The study participants consisted of 8 ultrasound proceduralists (RR, ARS, AMM, CO, SL, WC, TN, CD) performing the procedures, with 2 physician observers (AMT, ER) during needle placement to watch for harm and, subsequently, 5 fluoroscopy image evaluators (FDA, MS, AB, MLP, JA) assessing the needle placements on the fluoroscopic images captured.

The US proceduralists were experienced interventional pain physicians with Certified Interventional Pain Sonologist certification and 5-20 years of experience in performing and teaching US-guided procedures. The average experience in performing and teaching US- guided procedures was 10.8 and 5.2 years, respectively.

All proceduralists performed at least 50 medial branch blocks previously with the techniques assessed. Similarly, the evaluators were experienced, internationally recognized interventional pain physicians with a mean of 9.4 years since their Fellow of Interventional Pain Practice certification and 9 to 36 years of experience in performing and teaching fluoroscopy-guided procedures.

3.4.3 Test Under Investigation

Three Different Approaches to Ultrasound-Guided Needle Placement at the Third Occipital Nerve (TON), and C3-C6 Medial Branches

Approach #1 (ES): US visualization of a series of cervical articular pillars (US probe in the coronal plane, with the needle approach out of a plane, from anterior to posterior), as described by Eichenberger and Siegenthaler(34,36,37).

Placing the cranial end of the transducer over the mastoid process allowed for visualization of the C1 transverse process after moving it slightly caudally and posteriorly. A slight rotation of the transducer made the C2 articular pillar and C2-3 joint line visible, while further sliding of the probe revealed the “hills” and “grooves” marking the location of the medial branch. Needles were inserted in TON, C3, C4, C5, and C6 in that order, from anterior to posterior, until the needle tip was visualized at the deepest point of the articular pillar. (Fig. 16a-d and 17a).

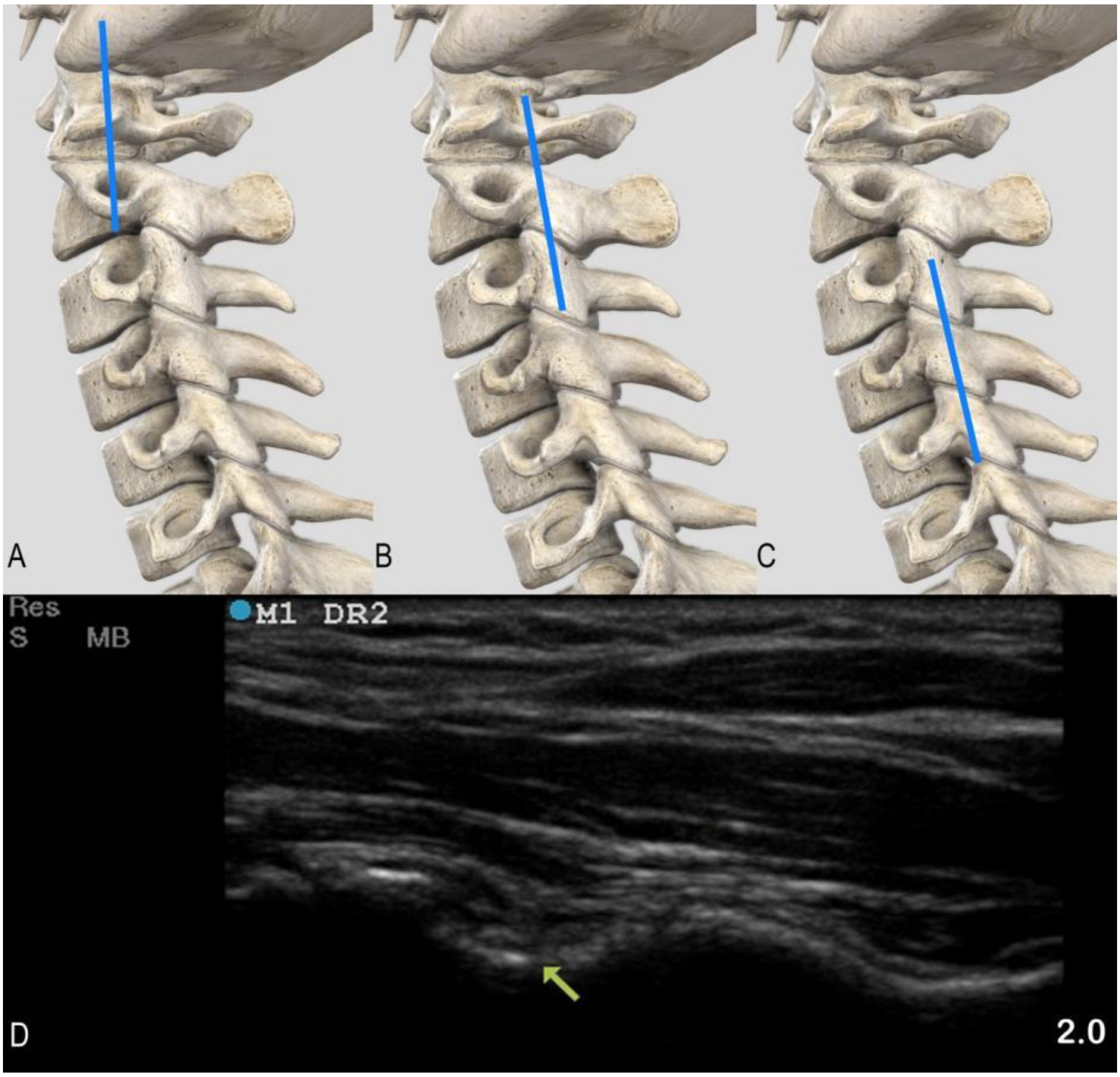

Figure 16. ES approach. US probe positions to identify TON and CMBBs. The cranial end of the transducer is placed over the mastoid process (blue mark), then it is moved slightly caudally and posteriorly to allow visualization of the C1 transverse process (A). With a slight rotation of the transducer, the C2 articular pillar and the C2-3 joint line come into view, which marks the target point for the TON (B). Sliding the probe further caudally

allows identification of the zygapophyseal joint openings, the “hills” and the deepest points of the articular pillars, and “grooves” marking the location of the medial branch (C). The typical wavy line of the articular pillar is visualized, the arrow marks the needle tip at C4 MB (D).

Figure 17. ES, Fi, FiM approaches, needles were placed to the TON, C3, C4, C5, and C6 medial branches, until bony contact was made. ES approach: out-of-plane technique, from anterior to posterior. The footprint of the US probe is visible on the cadaver (A). Fi and FiM approach: in plane technique, from posterior to anterior (B).

Approach #2 (Fi): US visualization of the cervical articular pillar and laminae (US probe in a slightly oblique transverse plane), needle approach in a plane, from posterior to anterior, as described by Finlayson (32) (Fig. 18a,b).

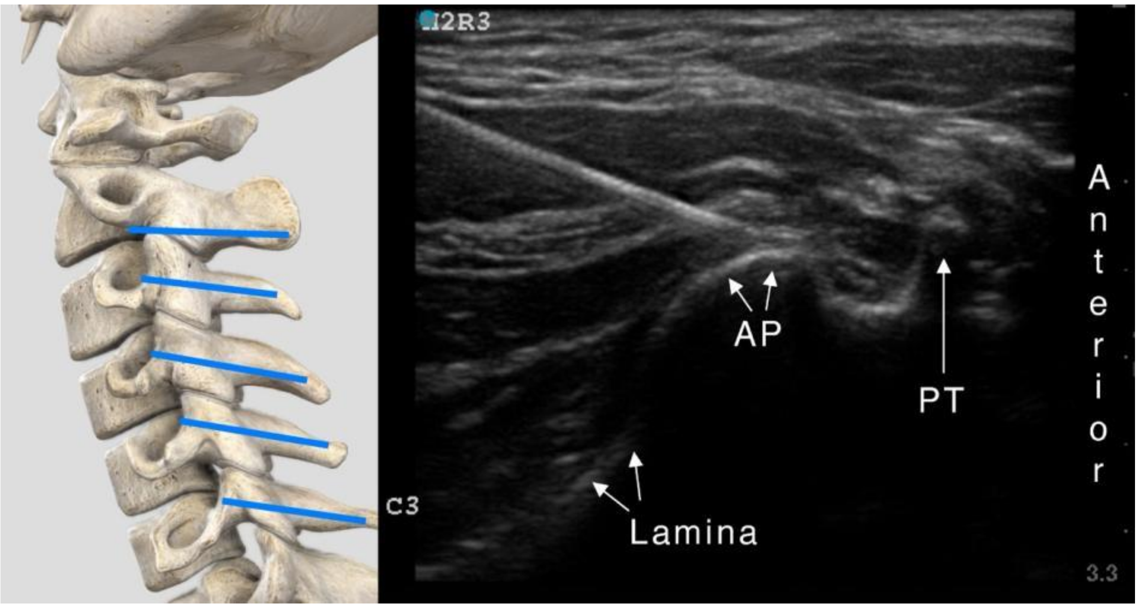

Figure 18. Fi approach. US visualization of the cervical articular pillar and laminae (US probe in the transverse plane with a slight caudal rotation, blue mark) (A). Needles were placed in the C6, C5, C4, C3, TON needle approach in plane, from posterior to anterior (B). The lowest point of the articular pillar, the lamina, and part of the spinous process are visualized. Needle on target at C3 MB. AP = articular pillar, PT = posterior tubercule (C)

Moving the transducer cephalocaudally the joint lines, “hills”, and “grooves” were visualized, marking the target point for MBB. Levels were identified by the characteristic tubercule/transverse process of C6 and C7. Needles were placed in the C6, C5, C4, and C3, TON order until bony contact was made at the deepest part of the articular pillar for C6-C3 and the C2-3 joint line for TON (Figure. 2B). Approach #3 (FiM): Needle placement as in Fi, then needle tip adjusted with US visualization of the C-spine in a coronal view, as suggested by Finlayson for TON, C5, and C6 levels. We hypothesized that a combination of the two views might show more precision at other levels as well (72) (Figure 19).

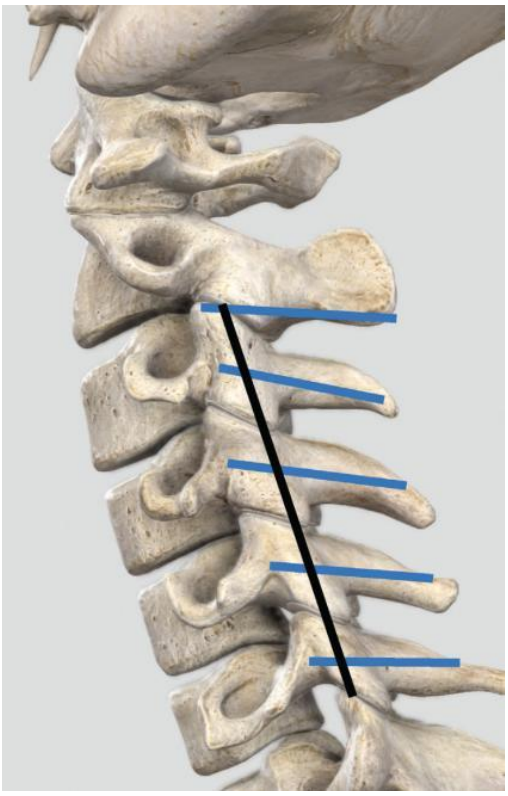

Figure 19. FiM approach. Target visualization and needle placement as in Fi (Figure 3), but then the needle tip was adjusted with US visualization of the C-spine in a coronal view (black mark).

3.4.4 Ultrasound-guided Procedure Description

Cadavers were positioned in lateral decubitus, optimal lateral, and anteroposterior x-ray imaging, with overlapping left and right articular pillars visible. After a 5-minute prescan, one practitioner placed needles at TON, C3-C6 medial branches using the ES approach, as well as Fi and FiM approaches. X-ray images were taken after each technique but not shown to the practitioner. This resulted in a total of 15 needles placed on one cadaver. No feedback was given between techniques. In total, 8 practitioners performed the procedure on 5 cadavers, leading to 165 needle placements.

3.4.5 Fluoroscopy Evaluation

Both AP and lateral fluoroscopy images of each needle were then evaluated independently for precision and safety by 5 experts. The evaluators were blinded to the proceduralist's name and other evaluator's assessment. These 2 standardly used fluoroscopy views are sufficient to reconstruct the 3-dimensional image of both the bony spine less the minor calcifications and the needle. Typical needle placement appeared as in Figure 20a,b for ES and Figure 21a,b for Fi and FiM.

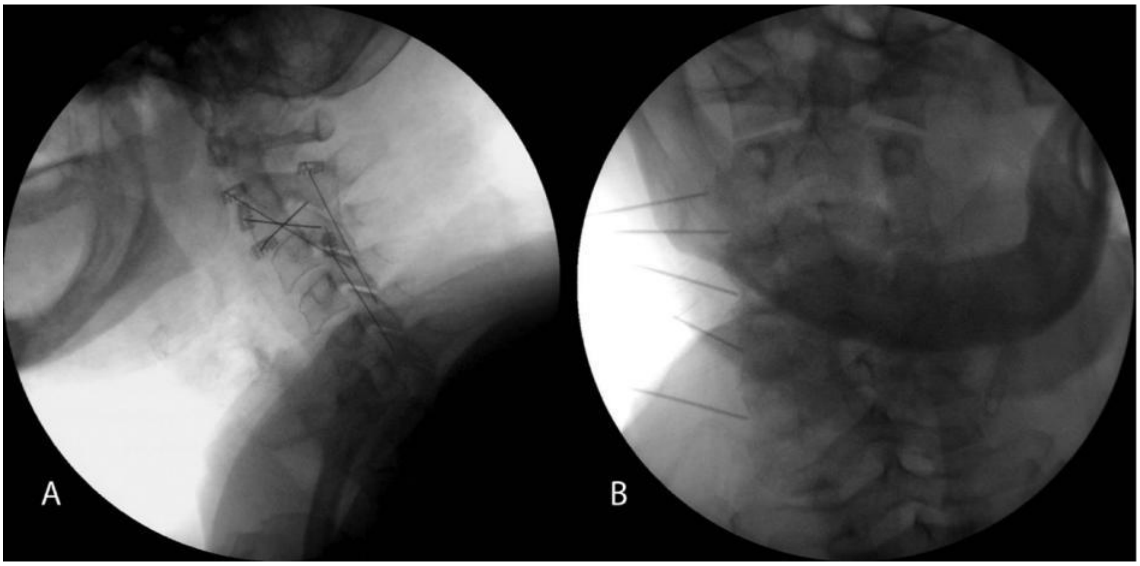

Figure 20. Fluoroscopy images for needle placement appeared for ES.

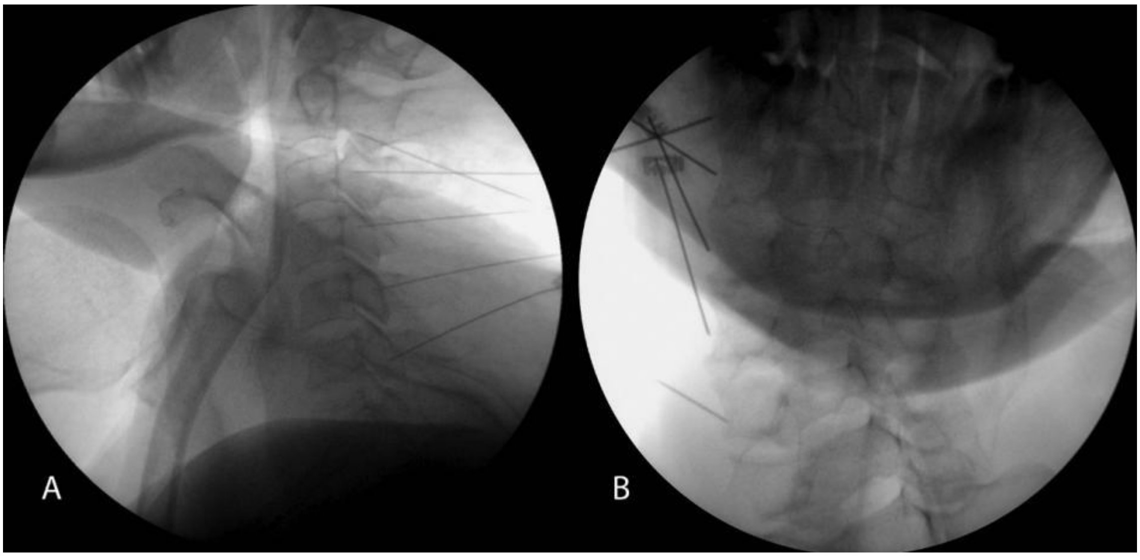

Figure 21. Fluoroscopy images for needle placement appeared for Fi and FiM

The specific questions evaluated were as follows:

1. "Is there a needle at the level, or is the level missed?" A missed level was defined as no needle tip identifiable on the lower portion of C2 or upper portion of C3 vertebrae for TON and on the corresponding vertebral levels for the C3, C4, C5, and C6 for MBB. If the level was missed, no further questions were asked.

2. "Is the needle in the joint line area (for TON)?" OR "Is the needle on the articular pillar (for C3, C4, C5, C6)?"

For the crude target, the area in the lower portion of the C2 and upper portion of the C3 articular pillar was defined as acceptable for TON, and the corresponding articular pillar was accepted for C3, C4, C5, C6, marked by the black dashed parallelogram (Figure 22).

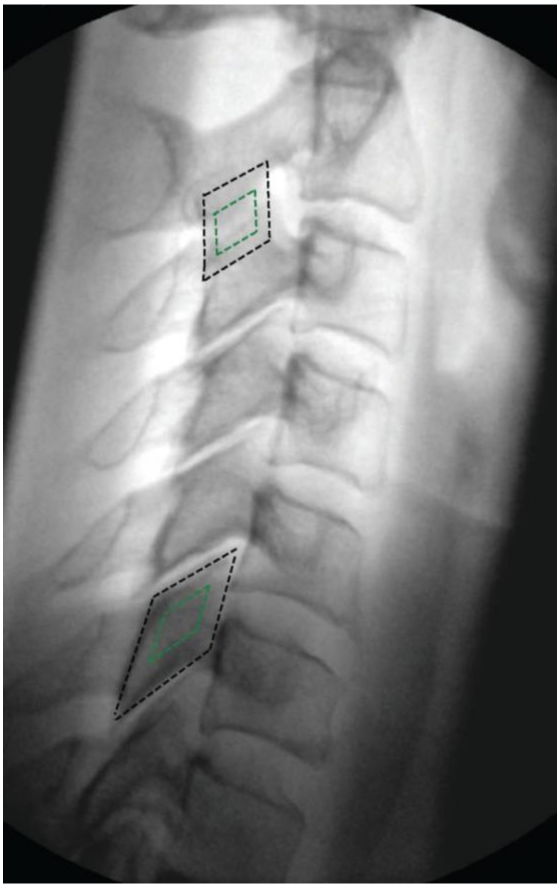

Figure 22. Evaluation of needle placement on the fluoroscopy images. For crude target, the area in the lower portion of the C2 and upper portion of the C3 articular pillar was defined as acceptable for TON, and the needle positioned on the corresponding articular pillar was accepted for C3, C4, C5, C6, marked by the black dashed parallelogram. For precise placement assessment, the needle tip in the green dashed parallelogram was accepted.

3.“Is the needle within the green zone?” For precise placement assessment, the needle tip in the green dashed (5 mm side) rhombus was accepted (Figure 22). We based this rhombus on the previously published papers by Siegenthaler et al. and the contrast spread at C2–C3 medial branch blocks studied by Barnsley et al(28). Finlayson also used the rhombus in his study to assess precise needle placement(33,34).

4. “Is the needle placement potentially dangerous?” Danger zones were defined as needles potentially compromising the spinal contents, the exiting nerve root, and/or the vertebral artery. In cases where there were 2 needles at one level, the needle in the better position was evaluated for precision, but both needles were assessed for safety/danger.

4 Results

4.1 Prolotherapy

26 neck and/or headache patients were treated during the study period. 24 patients filled out the questionnaire. The average number of prolotherapy sessions was 4.5 {range 4 to 8}. Average VAS scores decreased from 6.5 to 2.9. 50%, 42% and 8% noted “a lot”, ”a little” and ”no” functional improvement after the therapy, respectively. Overall percentage improvement of greater than 80% was reported by 38% of the patients, 50-79% improvement by 21%, 25-50% by 33% and less than 25% by, 8% of the patients. (Figure 23)

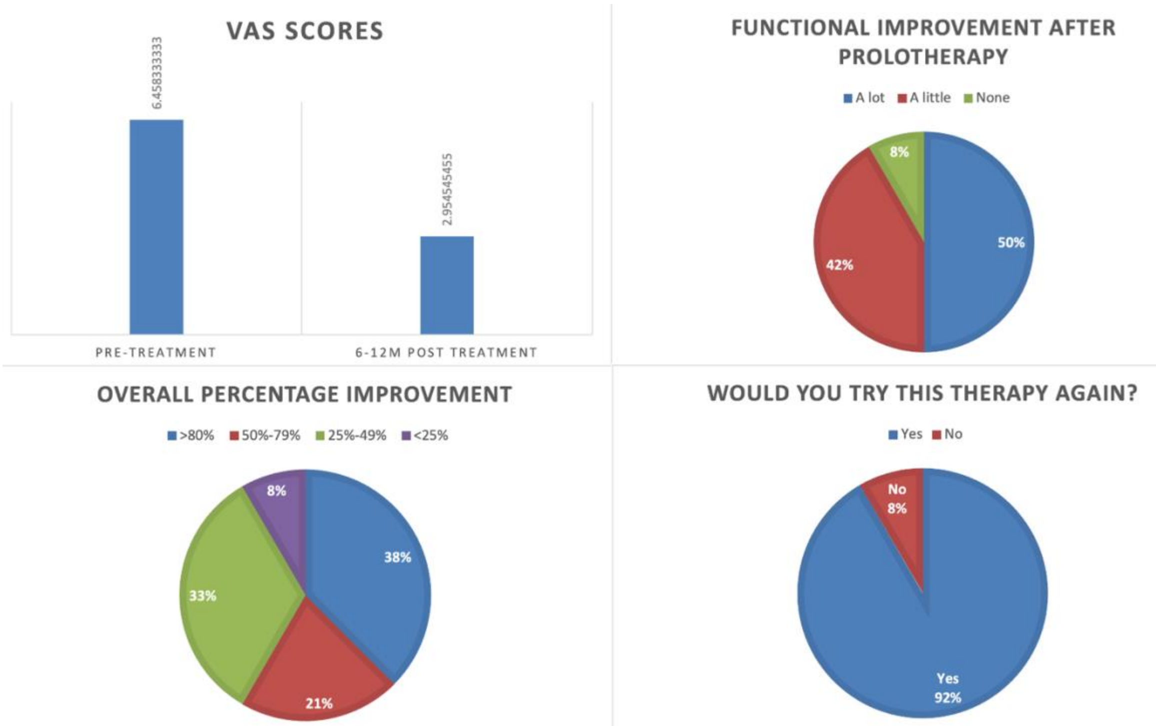

Figure 23. 24 out of 26 patients answered the questionnaire. Average VAS scores decreased from 6.5 to 2.9. 50%, 42% and 8% noted “a lot”,” a little” and ”no” functional improvement after prolotherapy. Overall percentage improvement of greater than 80% was reported by 38% of the patients, 50-79% improvement, 25-50% by 33% and less than 25% by, 8% of the patients. Image courtesy of Agnes Stogicza MD.

The 62-year-old patient presented above improved from baseline to 18 months in all self-reported and exam-based outcomes. Improvement in most outcomes began at the 2-week follow-up: at that time, the patient showed improved ROM in flexion, extension and rotation. Palpation tenderness did not markedly change compared with initial assessment, although the patient stated an overall decrease in tenderness. On self-reported outcomes, the patient reported decreased pain intensity (from 5 to 1 point on the VAS), and decreased disability (from 52 to 22% on the Oswestry Disability Index) by the fourth treatment and these results were sustained at the 18-month follow-up. The patient reported dramatic improvements in depression, anxiety, sleep, overall quality of life and satisfaction with care (Figure 20). No prescription medications were used, and pain-related healthcare use dropped to none during the 18-month treatment and follow-up period. The PainTracker tool facilitated point of care assessment during baseline and follow-up visits.

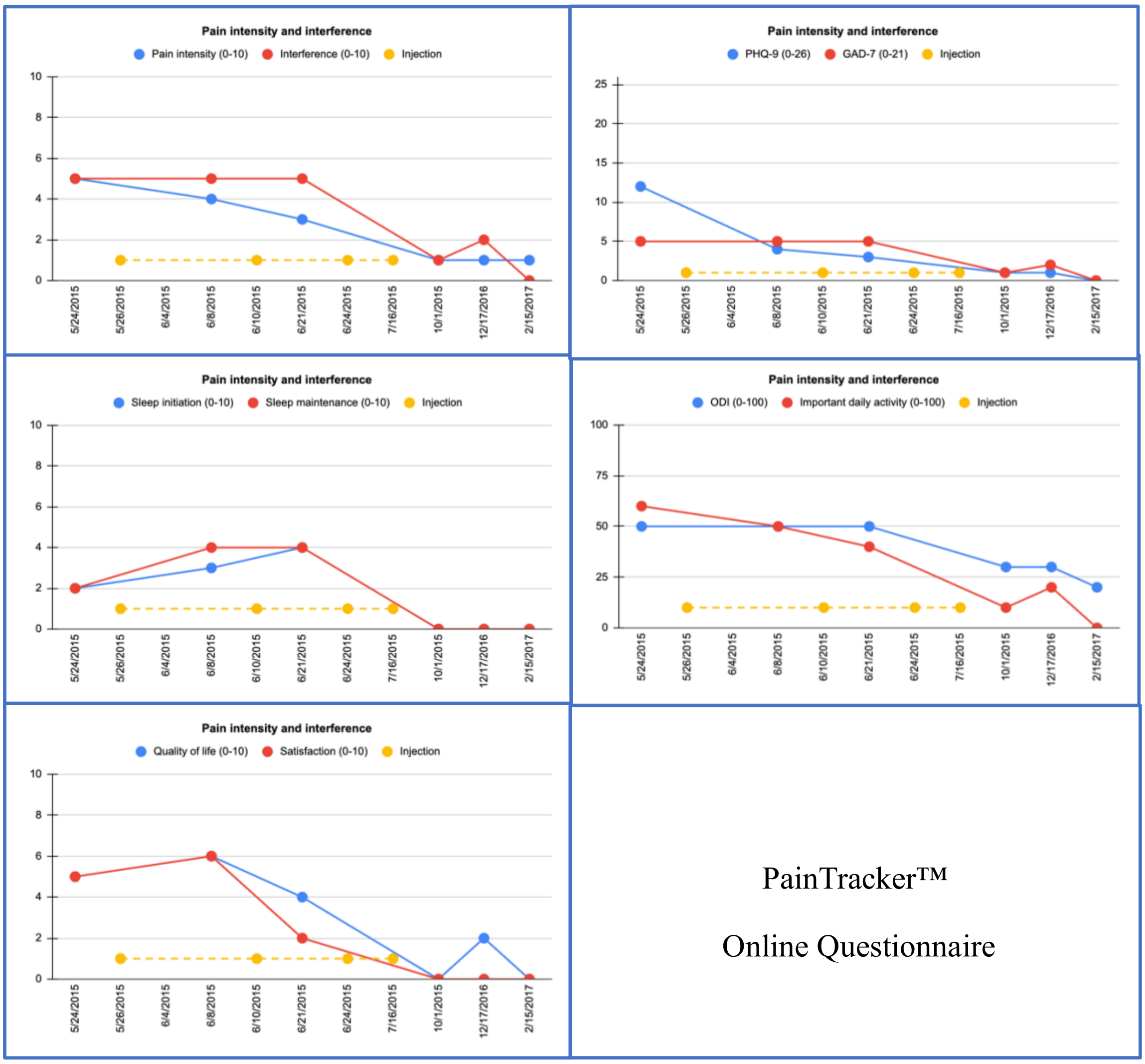

Figure 24. Outcome measures during 18-month follow-up as shown through the PainTracker™ online questionnaire. Lower scores indicate symptomatic improvement. Improvement is shown in Pain Intensity and Interference with daily functioning, depression, sleep, Oswestry Disability Index, Quality of Life and Satisfaction. Treatment started on 24 May 2015 and follow-up ended 15 February 2017. GAD: General Anxiety Disorder; ODI: Oswestry Disability Index; PHQ: Patient Health Questionnaire. Image courtesy of Agnes Stogicza MD.

4.2 PRP

The 7 patients who were tracked with NDI and VAS questionnaire underwent PRP treatment of the C spine, supplemented with medial C1-2 procedure (also referred to as PICL=percutaneous implantation of craniocervical ligaments procedure) reported and average of 39- point improvement on the NDI, and 5.2 point improvement on VAS score, 5 patients whose 12 month data already collected, sustained at more than 12 month and 2 patients sustained at 3 month (Figure 25). Data collection is still ongoing.

Figure 25. The 7 patients who underwent PRP treatment of the C spine, supplemented with PICL procedure reported an average of 39-point improvement on the NDI, sustained at 3-35 month (average: 18M) (A) and an average of 5.2-point improvement on the VAS score, also sustained 3-35 month (B). Patient #1,2,3,4,5,6,7 are represented by the colored lines. Data is collected electronically; red triangles and dates mark the regenerative interventions. Image courtesy of Agnes Stogicza.

Statistical analysis

Due to the low number of data, although collection is still ongoing, we performed a nonparametric permutation test, and data samples were iterated 5000 times to create Gaussian distribution. One-way ANOVA was used, corresponding p value was 0.05. During posthoc analysis, Bonferroni correction was applied.

NDI: One-way anova showed $F=5.0631$, $p < 0.0100$. There was significant reduction in the individual neck disability scores for one year follow up. The analysis suggested the changes became relevant 3 and 6 month after the treatment, and the process continued 1 year later. However, posthoc analysis with Bonferroni correction showed only significant changes in 1-year follow-up (pbonf.corr < 0.0026, Effect size: 2.46, respectively)(Figure 26).

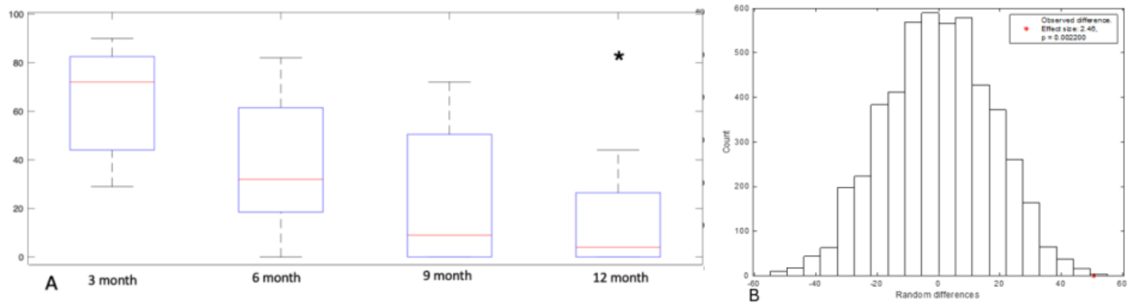

Figure 26. Box-plot demonstrates a significant decrease in NDI scores (A), Groupwise comparison of the baseline and 1-year follow up (B).

VAS: Similar method was applied in the case of VAS score. One-way ANOVA resulted F = 8.4902, p < 6.0000e-04 respectively, presented relevant decrease in the individual pain score variabilities. Posthoc analysis suggested significant pain score reduction after 6 month (Effect size: 2.07, p < 0.003799) and 1-year (Effect size: 3.54, p < 0.000200) (Figure 27).

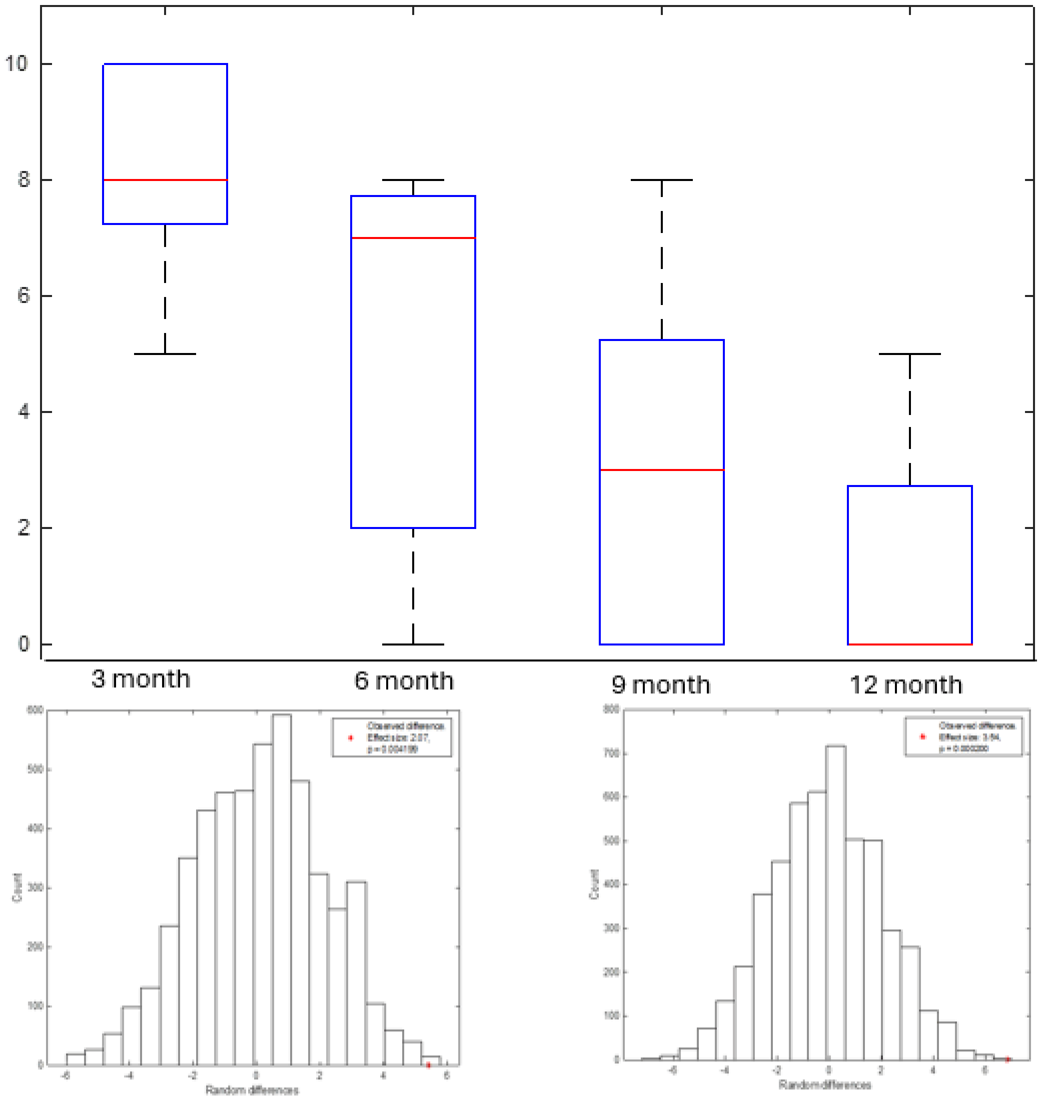

Figure 27. Top row presents the between-group comparison, '*' symbol indicate the significant changes. First bottom-line diagram shows the randomized distribution of the baseline and 6-month, second bottom line diagram shows the baseline to 1-year follow up data point with the corresponding statistical results.

Our representative case, the 33-year-old WAD patient (patient#1, blue mark on Figure 25), who underwent PRP treatment of the cervical spine and craniocervical junction noted 80% relief a month after the first treatment, and over 90% relief after the second treatment. Neck Disability Index value decreased from 36/50 (72%) to 2/50 (4%) 2 years after last intervention. Patient returned to full function, currently, 2 years after the last treatment cares for family and attends 3rd year medical school. She has occasional non-disabling headaches.

4.3 GON cryoneurolysis

With the above-described technique, we have performed cryoneurolysis of the GON more than 50 times at UW and further 6 in Hungary, treating both unilateral and bilateral occipital neuralgia. There have been no major complications. Minor complications were rare, consisting only of post-procedure soreness, which resolved spontaneously in 1 to 3 weeks. Slight numbness was confirmed at the GON distribution area that also spontaneously decreased within 1-2 months.

4.4 CMBB injection

A total of 5 cadavers were used for TON, C3, C4, C5, and C6 CMBB procedures resulting in a total of 165 needle placements. Ten needle placements were excluded from the study, as the AP fluoroscopic views were not saved for further viewing. Therefore, a total of 155 needle placements were assessed. Results are summarized in table 2.

All locations combined	ES-A n = 55	Fi-A n = 50	FiM-A n = 50	*P*-value
Level missed	6 (10.9%)	6 (12.0%)	5 (10%)	0.948
Correct crude needle placement	38 (77.6%)	35(79.5%)	34 (75.6%)	0.911
Placement within green zone	21 (42.9%)	10 (22.7%)	11 (24.4%)	0.032
Dangerous placement	3 (5.5%)	0 (0.0%)	0 (0%)	0.042
Third occipital nerve	n = 11	n = 10	n = 10	
Level missed (no needle at level)	2 (18.2%)	1 (10.0%)	1 (10.0%)	
Correct crude needle placement	3 (33.3%)	4 (44.4%)	5 (55.6%)	
Placement within green zone	3 (33.3%)	2 (22.2%)	3 (33.3%)	
Dangerous placement	2 (22.2%)	0 (0.0%)	0 (0.0%)	
Medial branch C3	n = 11	n = 10	n = 10	
Level missed (no needle at level)	1 (9.1%)	0 (0.0%)	1 (10.0%)	
Correct crude needle placement	9 (90.0%)	8 (80.0%)	6 (66.7%)	
Placement within green zone	3 (30.0%)	3 (30.0%)	3 (33.3%)	
Dangerous placement	1 (10.0%)	0 (0.0%)	0 (0.0%)	
Medial branch C4	n = 11	n = 10	n = 10	
Level missed (no needle at level)	0 (0.0%)	1 (10.0%)	0 (0.0%)	
Correct crude needle placement	11 (100%)	8 (88.9%)	8 (80%)	
Placement within green zone	6 (54.5%)	2 (22.2%)	2 (20.0%)	
Dangerous placement	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Medial branch C5	n = 11	n = 10	n = 10	
Level missed (no needle at level)	1 (9.1%)	0 (0.0%)	0 (0.0%)	
Correct crude needle placement	8 (80%)	10 (100%)	8 (80%)	
Placement within green zone	4 (40.0%)	1 (10.0%)	2 (20.0%)	
Dangerous placement	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Medial branch C6	n = 11	n = 10	n = 10	
Level missed (no needle at level)	2 (18.2%)	4 (40.0%)	3 (30.0%)	
Correct crude needle placement	7 (77.8%)	5 (83.3%)	7 (100%)	
Placement within green zone	5 (55.6%)	2 (33.3%)	1 (14.3%)	
Dangerous placement	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Null hypothesis: all are the same.

Table 2. Characteristics of needle placement stratified by method for all locations combined and separate.

Statistical Analysis

Characteristics of cadavers were described as mean and SD for continuous variables, and absolute value and percentage for categorical variables. As a measure of internal validity, we used the Fleiss' Kappa coefficient to compute agreement between observers who scored needle placements corrected for chance agreement. In case of disagreement between observers on needle placement, we took the most frequent binary score to end up with a single score within the procedure and location. For each method, we described the frequency of correct needle placement on the crude target, needle placement within the green zone, dangerous needle placement, and level/s missed. The various approaches were compared to each other concerning crude needle placement (dashed, black parallelogram), placement within the green zone, dangerous placement, and level missed using generalized linear mixed-effects regression to account for clustering of multiple procedures within cadavers.

Interobserver Agreement

Interobserver agreement on the safety of needle placement between the 5 observers was very high; Fleiss' Kappa was 0.923. Table 1 shows characteristics of needle placement stratified by method (ES, Fi, and FiM) for all locations combined and for all locations separately.

Precision

We did not find a significant difference in needle placements between the approaches on the crude tar- get (joint line and articular pillar) zones (ES: 77.6%, Fi: 79.5%, and FiM: 75.6%, P = 0.911).

The ES resulted in significantly more needle placements in the predefined green zones (ES: 42.9%, Fi: 22.7%, and FiM: 24.4%, P = 0.032).

Potentially Dangerous Placements

The total number of potentially dangerous needle placements was 3 with ES (needle potentially compromised both the exiting nerve root and the vertebral artery) (Figure 8), 0 with Fi and FiM.

Overall, ES resulted in statistically significantly more dangerous placement than Fi and FiM approach- es. (5.5% vs 0% vs 0% respectively, P = 0.042). Post-hoc analysis also revealed a significant difference between ES and Fi (P = 0.047), as compromising the vertebral artery and exiting nerve root only happened with ES.

Target Level Missed

Target levels were missed 6 (10.9%), 6 (12.0%), and 5 (10.0%) times with ES, Fi, and FiM, respectively. This difference between methods was not statistically significant. In a few cases, operators missed the most cephalad level (TON, ES approach), which resulted in all 5 needles placed one level caudad from the level intended (e.g., needles placed from C3-C7 instead of TON to C6), as the previously placed needle was used as reference. In cases like this, the data suggests only one level missed (TON); however, in real life, this would mean the operator would be wrong at each MBB. With that in mind, the total missed levels would have been 24.4%, 12.0%, and 10.0% with ES, Fi, and FiM, respectively.

5 Discussion

WAD is a challenging pathology to diagnose. Cervical injury from WAD, genetical factors or postural changes leads to a variety of symptoms, like headache, neck pain, shoulder pain, cognitive issues, fatigue etc., that make the diagnostic path often difficult. Patients may have multiple doctors' appointments without finding efficient treatment, resulting in significant health care costs. It is important that one recognizes that the constellation of the symptoms is the result of cervical instability. The instability in itself causes changes in the cervical curvature, leading to overloading the facets, discs, and eventually compromising the exiting nerve roots or in more advanced cases, the spinal cord.

WAD, non-responsive to conservative therapies is also a therapeutic challenge. Most treatment options (cervical medial branch block, third occipital nerve blocks, greater occipital nerve blocks have been shown to decrease pain only short term usually 3 months), but not necessarily decrease disability and healthcare use. Steroids are commonly used, but typically steroid naïve patients respond well temporarily, however repeated steroid injection leads to progressively shorter relief, until no relief at all provided. Furthermore, steroid has been shown not to have disease modifying effect in non-autoimmune musculoskeletal diseases, or to worsen outcomes on the long run (73,74). Moderate evidence exists supporting the efficacy of radiofrequency neurotomy in treating whiplash-related pain, and the relief it provides is not permanent. Sterile water injections have been found to be more effective than saline injections, but the actual benefits of this treatment remain uncertain. The effectiveness of botulinum toxin injections and cervical discectomy and fusion is surrounded by contradictory evidence. Overall, the current evidence is not robust enough to establish the effectiveness of these treatments. Among invasive interventions for chronic whiplash-associated disorder (WAD), radiofrequency neurotomy appears to be supported by the strongest evidence.(48)

The current study discussed novel approaches and novel procedures like prolotherapy and cryoanalgesia in the recovery from neck pain, headache and shoulder pain, associated with whiplash injuries. It also reviewed the available literature on minimally invasive treatment approaches available for WAD. Finally. It compared two commonly performed US guided median branch injection techniques for precision and safety.

Firstly, the thesis discusses a novel diagnostic approach whereby the cervical spine is viewed as a biomechanical unit, rather than an addition of pain generators that can result in chronic pain. With this approach it is recognized that some flexion extension injuries, typically the ones that fall in the WAD 2,3 severity category may result in a cervical spine instability (microinstability) from the ligamentous and capsular injury or shoulder instability, which then results in chronically increased muscle tightness, myofascial pain, nerve entrapment and faster degeneration of the spine or shoulder joint with chronic pain on the longer term (8). These patients may or may not present with immediate and typical symptoms and routine ER evaluation and imaging often does not give an explanation to the symptomatology described by the patient. They are then easily left with various levels of disability without finding adequate treatment, continuously using healthcare resources.

With this concept in mind, it may be possible to treat the underlying cause, namely the instability of the cervical spine, the craniocervical junction or the shoulder with regenerative medicine approaches.

Here we presented 24 prolotherapy cervicogenic headache cases with WAD and disability, successfully treated with regenerative medicine. All patients had similar symptomatology, similarly refractory to standard treatments, and had successful treatment with regenerative medicine. Another unique aspect of these cases was the long-term follow-up and sustained results.

Prolotherapy was part of the routine treatment at University of Washington to cervicalgia and cervicogenic headaches in cases refractory to more standard approaches like facet joint steroid injections, medial branch blocks and radiofrequency denervation. Because of the strong cooperation of the UW Headache Center and the Center for Pain Relief, during a 7-year period, conservatively counting we performed over 200 cases. The retrospective review was performed in 2014 and assessed 24 patients, 59% of whom reported greater than 50% pain improvement. Online data collection (Pain Tracker) (67) however only became available later, hence the report published only discussed a single case. However, the case is representative of the cohort. It is relevant owing to long-term follow-up, the variety of outcome data collected, and the scarcity of medical literature related to regenerative medicine techniques in the treatment of WAD. The patient underwent fluoroscopy guided P2G prolotherapy as described above and reported improvements in different measures. These included pain intensity, mood, quality of life, and activity of daily living. All these measures were sustained for a period of 18 months. These treatment outcomes were otherwise refractory to other standard-of-care procedures for a duration of up to 14 months. After the treatment the patients reported no further use of healthcare services during the follow-up period of the study, suggesting that the intervention had outstanding outcomes for this patient suffering from chronic pain. Another novelty in this case is the use of regenerative medicine to the craniocervical junction, namely the AA and AO joints (75).

Further 7 WAD patients were treated with PRP at the cervical spine (facets, supraspinous ligaments, AA, median and lateral AO joints) and tracked with electronic automated data collection system. They achieved a significant improvement in the NDI scores, decreasing from average 64.7% to 25.7%. The female presented as representative case had a complete return in function, despite failing multiple therapies for 3 years pretreatment. This also emphasizes the need to identify treatable causes prior to assigning psychological and psychiatric diagnoses.

A possibly highly efficient treatment modality for patients suffering from chronic musculoskeletal diseases and WAD is regenerative medicine. Regenerative medicine, which includes prolotherapy, platelet rich plasma or stem cell injection has a rapidly growing body of literature, with over 17600 peer reviewed publications available on pubmed, with 1150 randomized controlled trials and 959 systematic reviews among them at the end of 2024 (76).

Prolotherapy and PRP treatment are minimally invasive injection-based treatments delivering a therapeutic solution at sites of painful and dysfunctional ligament or tendon insertions and joint spaces. The core principle of the administration of prolotherapy or PRP injection is the use of a small quantity of solution, ranging from 0.2-0.5 mL, for injecting into the attachments of ligaments and tendons as well as into the affected joint spaces. The dextrose solution that is commonly administered in prolotherapy interventions contains 0.25% lidocaine and 15% dextrose. The typical prolotherapy treatment comprises a minimum of three treatment sessions for the administration of prolotherapy injections, each one month apart. However, the intervals between each injection may range from two weeks to six weeks (77). PRP is administered in a similar manner, however usually a smaller number of treatments is needed to achieve similar results.

In these cases, P2G (dextrose 15%, phenol 0.5% and glycerin 2.5%) and PRP were used. Injection of irritant substances or direct platelet injection is thought to produce an inflammatory response followed by a natural healing cascade stimulating tissue regeneration with subsequent improvement in joint stability and reduced pain. Although the precise mechanism of prolotherapy is not known, in vitro models have shown cell proliferation following initial prolotherapy-induced cell death (78–80). Multiple contributing mechanisms have been suggested, for example: mechanical transection of cells induced by the needle itself and disruption of the cells by the hyperosmolar extracellular volume that may induce the inflammatory response conducive to healing. Compression of the small nerve fibers have also been postulated in the mechanism of pain relief (81).

PRP is a natural source of signaling molecules, and upon platelet activation the P granules degranulate. This gives rise to various growth factors that change the pericellular microenvironment. The most important GFs released by the platelets are the vascular endothelial GF, fibroblast GF (FGF), platelet-derived GF, epidermal GF, insulin-like GF 1,2, matrix metalloproteinases 2, 9, and interleukin (51).

Therefor while prolotherapy initiates the inflammatory cascade via cell injury, lipid leakage and thrombocyte activation, the same process can be initiated by direct autologous thrombocyte injection (Figure 28).

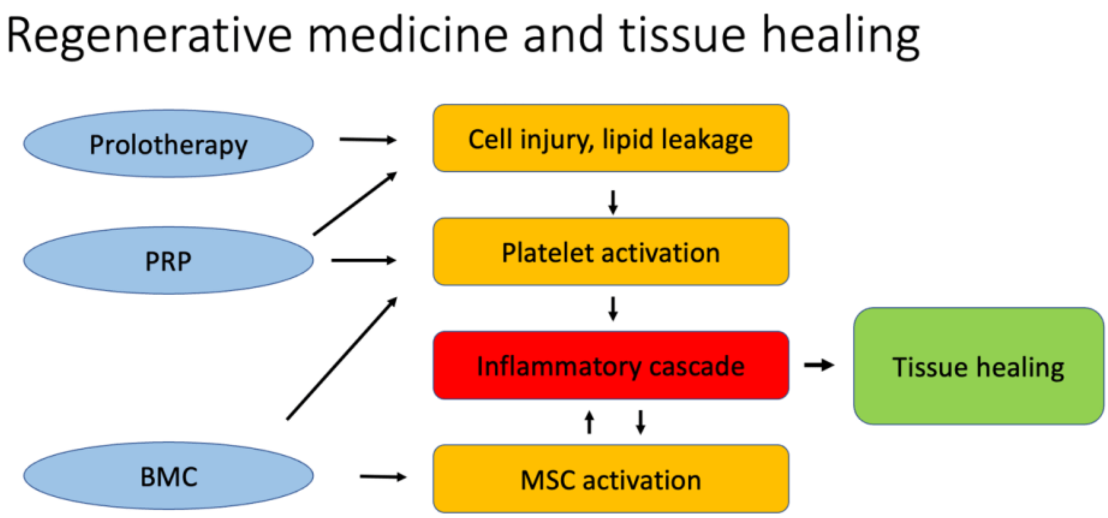

Figure 28. Prolotherapy initiates the inflammatory cascade via cell injury, lipid leakage and thrombocyte activation. The same process can be initiated by direct autologous thrombocyte or bone marrow concentrate (MSC+ PRP) injection. Image courtesy of Agnes Stogicza MD.

The majority of high-quality clinical evidence for prolotherapy comes from studies of peripheral joint disorders including knee OA prolotherapy (82–85) and tendinopathies including lateral epicondylitis (86) showing improved pain, function and patient satisfaction. A recently published systematic review of 14 randomized controlled trials, one case control and 18 case series showed dextrose prolotherapy to have benefits in tendinopathies, knee and finger joint OA, and spinal/pelvic pain due to ligament dysfunction (62).

Similarly, for PRP the most studies with highest quality have been assessing PRP use for knee OA and lateral epicondylitis probably owing to its high prevalence and relatively low risk in treatment. PRP provides good, sustained improved function and pain reduction for knee OA as demonstrated by multiple RCTs and metanalysis and systematic reviews of the available literature (87–89). Furthermore, a wealth of compelling evidence supports the application of LR-PRP injection in addressing lateral epicondylitis and LP-PRP for managing knee osteoarthritis. There is also substantial and reliable evidence indicating the effectiveness of LR-PRP injection in treating patellar tendinopathy, as well as the use of PRP injection for alleviating symptoms of plantar fasciitis and donor site pain in patellar tendon graft BTB ACL reconstruction. However, the evidence is not strong enough to consistently recommend PRP for conditions such as rotator cuff tendinopathy, hip osteoarthritis, or high ankle sprains. The existing data indicates a lack of efficacy of PRP in addressing Achilles tendinopathy, muscle injuries, acute fractures or nonunion, and surgical augmentation (90).

Level I studies back the use of PRP and MSC injections for low back pain. PRP and MSC for discogenic pain(91,92), PRP (93,94) and prolotherapy, for facet joint arthropathy and sacroiliac joint pain(95). One Level I study indicated that facet joint prolotherapy lacks significant benefits, however during the placebo treatment (saline injection) all facet joints and several locations along the iliolumbar and posterior sacroiliac ligaments were injected. Any tissue trauma triggers the inflammatory cascade so the sham group rmay have also received an active treatment. Notably, both the active and the sham group achieved significant benefit, that was sustained over a year (96). PRP preparation is heterogenous throughout the studies, however as a general guideline, low leukocyte, high platelet count is required for benefit in joint OA and high platelet count with high leukocyte concentration is beneficial for tendinopathies (97).

Evidence supporting prolotherapy or PRP for neck and cervical pain remains limited to case series and case reports describing non validated self-reported outcomes. One study followed 98 patients with unresolved neck pain treated with 15% dextrose and 0.2% lidocaine for 18 months, reporting that 89% of patients experienced over 50% pain relief, 72% discontinued pain medications and 97% with increased quality of life (98). Another study followed 147 patients with chronic cervical, thoracic or lumbar pain and joint laxity demonstrated on stress test – given weekly injections of dextrose 20% for up to 3 weeks. Results showed 90% of patients with symptom and functional improvement, 76% with improved ability to work and 82% with decreased medication use (95). Hooper treated patients with intraarticular prolotherapy by placing 0.5 – 1mL of 20% in a retrospective case series of 18 patients and shown similar improvements in pain, function, ROM and overall satisfaction (45). Finally, Centeno demonstrated a reduction in cervical flexion and extension translation and VAS after facet joint intraarticular prolotherapy injection (99). A recent study showed no difference at 6 month treatment between steroid and PRP in the cervical facet joint (100), however they admittedly used low platelet count, which is already known to have lesser to no effects (101). 44 people underwent cervical facet PRP injections in the prospective case series by Smith et al and demonstrated significant (>50%) and sustained improvement in NDI and VAS (102). Sustained relief is crucial, as the life span of these patients does not differ from normal populations, and previous treatments like steroids had no long-term benefit. Repeated steroid use provides shorter and shorter pain relief, yet the obvious side effects cumulate.

The cases series presented in this work are representative of our more than 15 years of experience with regenerative treatment for over 200 patients with cervicogenic headaches, WAD and cervicalgia. It builds on the concept that WAD and cervicogenic headache are biomechanical problems, and the targets to treat are selected accordingly. The injection of the craniocervical junction with an orthobiologics is newly published, and also the length of follow up is unique to our cases (75). Recent randomized controlled and prospective case series by Kirchner and Atluri on lumbar spine used the same concept for treatment (ligaments, tendons, discs and facets are treated as a biomechanical unit), and resulted in outstanding, sustained positive outcomes (89–91).

Direct comparison with the current cases is limited by variable inclusion criteria, varied treatment protocols and lack of information on use of concomitant therapies by the participants.

In the cases where regenerative approach is not feasible, cryodenervation of the painful area after positive diagnostic block may still provide an answer to decrease pain and disability and improve function.

Headache, occipital neuralgia or occipital nerve entrapment may be caused by trauma, fibrositis, myositis, AA lateral mass osteoarthritis and may be the leading symptoms of WAD.

There are a variety of minimally invasive treatments used for occipital neuralgia, including steroid injections, pulse radiofrequency, cryoneuroablation, radiofrequency ablation, occipital stimulation, and C2 gangliotomy, all of which have been performed with some success (106–110). Gille and colleagues showed that neurolysis of the GON and sectioning of the IOCM at C2 was highly successful when performed in selected patients (111). Steroid injections, pulse radiofrequency, and cryoneuroablation are often done at the nuchal ridge, just medial to the occipital artery. This "classical" approach, although relatively safe and easily performed, is not target specific, and usually requires larger amounts of local anesthetic. The injection might involve the other nerves in the vicinity (eg, the lesser and third occipital nerves), and therefore it loses its diagnostic value (112). Greher et al. described a more proximal US-guided injection technique between the C1 transverse and C2 spinous processes just above the IOCM, where the occipital nerve is clearly visible with US (see Methods) (113). This latter technique allows for precise needle placement, along with a selective diagnostic block. It is important to recognize that, the third occipital nerve lies only a short distance away, it is often also anesthetized, even with small volumes (112), which then may lead to false positive diagnostic block, followed by less satisfactory results with the ablative technique. Also, as the occipital nerve has a marked anatomic variability and often splits to several branches before reaching the nuchal ridge (114), this proximal technique allows capturing most of the branches, prior to the splitting of the nerve. We reported an US-guided cryoneuroablation technique for unilateral or bilateral greater occipital neuralgia and headache performed at the proximal location. This new, proximal US-guided cryoneuroablation approach has several advantages compared to the classical, more distal one. US for GON allows easier visualizations just posterior to the IOCM. In addition, the IOCM overlies the bony shadow of the C2 lamina confers improved safety when performing this technique, eliminating any possibility of inadvertent spinal cord or vertebral artery puncture. At the C2 level, which is below the hairline, skin disinfection is easier, and shaving is normally not necessary. Here, the nerve is deeper, lying between tissues that have a distinct sonographic appearance, without bony artifacts and not in close proximity to an artery. Proximal blockade of nerves often provides better results than the distal approaches, especially in occipital neuralgia, where nerve entrapment may be proximal.

Cervical medial branch injections are commonly used to treat headaches, neck pain, and shoulder pain. Precise injection is essential to optimize effectiveness and reduce potential complications, especially given the high-risk areas in the neck. Two groups have made significant contributions to

cervical facet approaches: the European Eichenberger- Siegenthaler group and the Canadian Finlayson group. Eichenberger and Siegenthaler introduced the ES technique after injecting 14 healthy, low BMI volunteers, and showed 90% accuracy (34,36,37), then showed shortened fluoroscopy-guided radiofrequency procedure time when the MB was localized sonographically pre-procedure (115). Siegenthaler could successfully visualize the C3-C6 MBs in 39 (78%) of 50 patients. However, the visualization was not confirmed in any way, and patients were not injected. In his next study, he placed 107 US-guided needles to the C3-7 MB of healthy volunteers and showed a 77% accuracy rate ("green zone") for needle position and 84% for contrast spread. However, the study population had lower age (median 25 years) and BMI (22) and likely no arthritic changes compared to the general neck pain population, which may impact the results. The other remarkable group of papers that we rely on came from Finlayson et al. He described the posterior to anterior an in-plane approach to the TON, C3-C7 MBB (31–33). In a randomized controlled trial, he compared US-guided TON procedures to fluoroscopy-guided procedures and found good numbness in the TON distribution area for 19 out of 20 patients. In his paper on the US-guided C3-C6 MBB with fluoroscopy (lateral view only) confirmation he achieved 100% success in placing the needle onto the articular pillar of interest ("crude targeting" in our study); however, positioning it on the center ("green zone" in our study) was achieved in only 80.9% of the cases. Of these cases, 19.1% (mainly at C6 and C5 levels), the needle tip was located on the outer edges of the articular pillar, which he explained as due to degenerative changes. He also raised the idea that it would not matter, since, despite these positioning results, he achieved a better contrast spread (100% for C3, 97% for C4, but only 91.4% for C5 and 84.9% for C6) to the targeted area with 0.3 mL solution of contrast and local anesthetic (33). To improve the success rate, he developed the biplanar technique (FiM) and achieved a 100% success rate on 40 patients, confirmed by contrast spread (72). Of note, all these procedures were performed by 2 proceduralists throughout the publications. In a randomized controlled trial, he compared US-guided TON procedures to fluoroscopy-guided procedures and found good numbness in the TON distribution area for 19 out of 20 patients. In this study, we compared the 3 above-discussed approaches to US-guided CMBB, with a focus on safety and precision.

Safety

The cervical spine has multiple structures of vital importance. Any errors during needle placement can lead to permanent damage or fatal consequences. Stroke, paralysis, spinal cord ischemia, vertebral artery compromise with cerebellar infarction, hematoma, high spinal anesthesia, and death have been reported (39). Based on the level of danger and the likelihood of occurrence during needle placement we focused on the most devastating consequences - a compromise of the intraspinal space, the vertebral artery, and the exiting nerve root. We found that ES is clinically and statistically significantly more dangerous than Fi and FiM (ES resulted in 3 exiting nerve root and vertebral artery compromise, whereas Fi and FiM led to none). There may have been multiple reasons for this: 1) With ES the ideal needle trajectory is barely different than a needle placed in the neuroforamen or in the spinal canal, so a slight error in identifying the coronal plane or in needle trajectory combined with the loss of depth control can result in foraminal or spinal space breach; 2) Higher BMI, and arthritic neck can increase the chances of loss of depth control (Figure 29). The cadaver necks were arthritic, making the landmarks harder to identify. This reflects real-life situations, unlike the way the ES was described on only healthy, young volunteers.

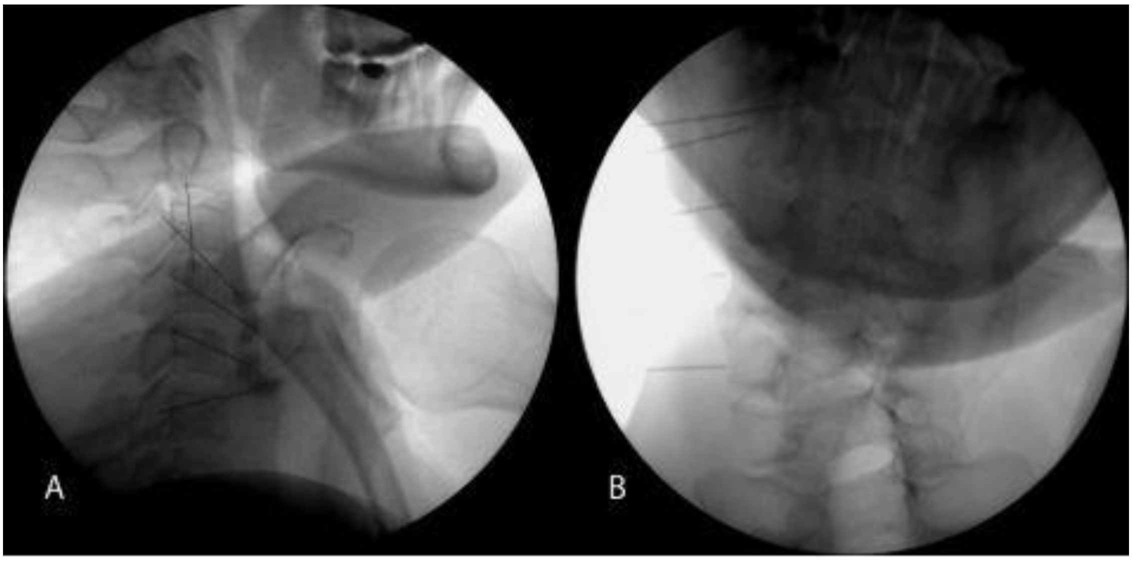

Figure 29. ES approach. Example of a needle placed more anterior than planned, and potentially compromised both the exiting nerve root and the vertebral artery. Lateral view A, AP view B.

Also, one must observe the natural shape of the articular pillars: the characteristic waveform can be observed both from lateral (coronal US probe placement, Figure 30a) and somewhat anterior (Figure 30b). Without a thorough understanding of the C-spine topography, it is easy to aim more anteriorly, hence, to target the posterior portion of the neuroforamen, instead of the lateral part of the articular pillar. This puts the vertebral artery and exiting nerve root at risk. Siegenthaler et al (36) suggested introducing the needle from anterior to posterior, as the vulnerable structures are situated more anterior to the facet joint line (i.e., vertebral artery and neuroforamen). In our opinion, nothing prevents the inexperienced proceduralist from placing the needle too anterior in the hunt for the target and the needle tip, especially in a patient with less ideal anatomy (shorter neck or higher BMI) which therefore exposes the vertebral artery, exiting nerve root and spinal cord to injury.

The posterior to the anterior approach of Fi has no vital structures in the needle trajectory, therefore it seems a safer approach, as also proven in our study. In real life, an awake patient would report nerve root violation, reducing the risk of additional damage and risk of access to the spinal canal. Nevertheless, spinal cord injury has been reported, as stated above (43).

Figure 30. The characteristic waveform utilized in ES can be observed both from lateral (green mark). (A) and somewhat anterior (orange mark). (B). The US probe positions for the corresponding US image are marked on the model's skin.

Precision For precision, we identified crude and precise positioning.

The lower C2 or upper C3 pillar for TON and the corresponding articular pillar for C3-6 MB were acceptable for crude targeting. This may result in sufficient local anesthetic spread to the medial branch as was shown by Finlayson (33). In our study, 77.6%, 79.5%, and 75.6% of the needles were acceptably placed for crude targeting in ES, Fi, and FiM approaches respectively, showing no significant difference. TON blocks had lower success rates, achieving only 33.3%, 44.4%, and 55.6% accuracy by ES, Fi, and FiM approaches. The success rate for the other levels with all approaches ranged between 77% and 100%. We have found that ES resulted in significantly more needle placements in the predefined green zones, i.e. the centers of the articular pillars (42.9% compared to 22.7% and 24.4% for the ES, Fi, and FiM, respectively). Previous studies recommended that the needle tip be placed in the centroid of the articular pillar for diagnostic blocks (115), and parallel with the joint lines on the articular pillar for radiofrequency ablation for effective denervation. More recent measurements of the cervical medial branches suggest that medial branch size and location vary. The C5 MB occupies the lateral concavity of the articular pillar with variation becoming greater at levels further from C5 (116). In light of the variations of the MB positions relative to the bony articular pillars, the relevance of the green zone may become questionable. Furthermore, the usually injected 0.3 mL for diagnostic injection usually covers the entire articular pillar at the given level (117). Approach #1: ES, is the most tempting for the novice proceduralist because the famous wavy line formed by the articular pillars can be reliably visualized with limited experience. This approach is not suitable for radiofrequency lesioning unless a special needle is used (tripod, bipod, cooled RF), as the small lesion at the tip of the needle is unlikely to incorporate the medial branch. Approach #2: Fi is somewhat harder to learn for new sonographers because it entails understanding the C-spine sonoanatomy in more detail. Recognition of the different shapes of each cervical lamina, caudally slanted spinous processes, and caudal rotation of the US probe are essential. However, once incorporated into scanning, the technique is easier and safer. The needle is placed in-plane, ensuring meticulous positioning while maintaining needle tip visibility. Furthermore, Fi is also useful for radiofrequency ablation, where the goal is to place the needle tip along the pillar to in-crease the chances of incorporating the medial branch in the lesion.

Approach #3: FiM was expected to carry the benefits of both ES and Fi; however, our data indicates the contrary. Any manipulation of the needle without perfect visualization of the needle tip does not add to the precision. Before the start of his study on the C3-6 MBB, Finlayson had evaluated (and abandoned) the use of a coronal plane to verify the position of the needle after the latter had been placed with a transverse plane(33). As also noted by Lee et al (118), it is difficult to reliably visualize a static needle in its short axis. Later, Finlayson showed that the C5 and C6 MB precision placement improved with biplanar visualization (72). In our study, the proceduralists misplaced the needle in more than 10 % of the cases, which may reflect poorly on the ability to judge the levels by the US. However, as by the nature of the needle placement method, one misplaced needle immediately results in missing the consecutive levels. Therefore, if all 5 needles were shifted caudally, we modified the score from 5 to 1. However, in real-life conditions, one can encounter a similar problem, when multiple needles are all placed to a different level than intended.

5.1 Strengths and Limitations of the Study

The study reviewed WAD and discussed a new potential paradigm to understand whiplash associated complex symptomatology. This understanding may open new therapeutic approaches to WAD and chronic cervicogenic headaches. Peripheral nerve ablation is well established, and the study added a novel ablative techniques to the literature to aid GON cryoablation. Regenerative approaches are well established for various chronic pain indications, however there is only limited low quality evidence to support its use in WAD. This work is the first to describe the use of orthobiologics in the craniocervical junction and is the first to provide long term data collection.

Main weakness is the heterogenicity of the treatment approaches, small patient number, inconsistent data collection. The study design and the limited number of study participants prevents the study authors to establish causality of the presenting complaints and generalize the study results for the entire population.

5.2 Key findings

The conceptualization of the cervical spine as a biomechanical unit, rather than an aggregation of separate pain sources.

Regenerative medicine may provide a solution to treatment resistant WAD, cervicalgia and cervicogenic headache.

Regenerative medicine may improve stability of the cervical spine by improving biomechanics.

Injection of the median C1-2 joint has been safely performed and led to clinical improvements in severe WAD.

Cryoablation of the GON at the level of the IOCM appears safe with precise ultrasonographic guidance. (novel technique)

Cryoablation of the GON improves treatment resistant cervicogenic headaches, occipital neuralgia.

Medial branch block performed according to Eichenberger-Siegenthaler are potentially more dangerous than that described by Finlayson, as danger zones (vertebral artery and exiting nerve root) are in the needle trajectory with the first approach. They seem equal in their precision in getting the local anesthetic spread to the appropriate site.

6 Conclusion

Whiplash associated disorders, and related headache and neck pain creates a pathophysiologic and diagnostic challenge, which also leads to a therapeutic challenge. Here we discussed the biomechanics of WAD and some new therapeutic options.

Regenerative medicine (PRP, prolotherapy) treatment options may address the underlying instability and therefore provide long-term solutions as shown in our retrospective review and prospective data collection.

In cases where regenerative medicine may not be available cryoablation of the GON decreases occipital headaches and is safely performed at the level of the IOCM.

The use of PRP and hypertonic dextrose at the craniocervical junction, the GON cryoablation at the proximal location posterior to the IOCM was first reported in the literature.

Cervical procedures are dangerous, high-risk procedures even in experienced hands, and they may compromise patient safety if anatomy is challenging because of, for example, advanced arthrosis. The currently taught and practiced CMBB methods both in-plane and out-of-plane (ES, Fi, and FiM) should yield a similarly successful block. However, the ES approach seems more helpful in placing the needle precisely on the centroid of the articular pillar, but it also leads to a greater number of dangerously placed needle tips. The 3 approaches are equally inadequate in identifying cervical vertebral levels, so the aid of fluoroscopy is still recommended to prevent those errors.

Further high-quality studies randomized controlled trials are needed to establish these procedures and prove their safety and benefit to WAD.

7 Summary

Introduction: Whiplash Associated Disorders (WAD) presents with complex symptomatology severely impacting quality of life. Minimally invasive interventions like prolotherapy and Platelet-Rich Plasma (PRP) injections may pain and function. Cryoablation offers relief for various nerve-, including greater occipital nerve (GON) entrapment in case of WAD. Cervical medial branch block (CMBB) have been utilized to alleviate cervical pain; however, data on the safety and accuracy of ultrasound-guided approaches are limited.

Objective: 1. To assess the efficacy of prolotherapy and PRP treatments for WAD, to review existing literature and to introduce novel, minimally invasive techniques to decrease pain and dysfunction. 2. Describe novel approach to cryoablation of the GON. 3. To evaluate the safety and precision of two ultrasound-guided approaches for CMBB.

Methods: 1. Retrospective review of prolotherapy data from 24 patients, a prospective pilot PRP study of 7 patients with cervical spine and craniocervical junction. 2. Ultrasound guided proximal GON cryoablation, a newly developed ultrasound-guided technique for treating greater occipital neuralgia. 3. A cadaveric study of 165 US guided needle placements for CMBB with fluoroscopy verification for safety and precision.

Results: Prolotherapy yielded significant improvements in pain scores (VAS scores decreasing from 6.5 to 2.9) and functional outcomes. PRP for the CCJ and cervical spine showed substantial improvement in neck disability index and VAS scores. Cryoablation of GON was successfully applied in over 50 cases. Out-of-plane, anterior to posteromedial CMBB demonstrated higher precision in targeting specific zones, though in-plane, posterior to anterior approaches avoided compromising critical structures.

Conclusion: regenerative treatments such as prolotherapy and PRP address cervical ligament instability, reducing pain and enhancing biomechanical function. Cryoablation of the GON and CMBB, especially in-plane, posterior to anterior approach, provide valuable options for patients unresponsive to other treatments, offering improvements in pain and quality of life. Further studies are necessary to expand the understanding and efficacy of these minimally invasive treatments in managing WAD.

8 References

1. Yadla S, Ratliff JK, Harrop JS. Whiplash: diagnosis, treatment, and associated injuries. Curr Rev Musculoskelet Med. 2008;1:65–8.
2. Côté P, Hogg-Johnson S, Cassidy JD, Carroll L, Frank JW, Bombardier C. Initial patterns of clinical care and recovery from whiplash injuries: a population-based cohort study. Arch Intern Med. 2005;165(19):2257–63.
3. Côté P, Cassidy JD, Carroll L, Frank JW, Bombardier C. A systematic review of the prognosis of acute whiplash and a new conceptual framework to synthesize the literature. Spine (Phila Pa 1976). 2001;26(19):E445–58.
4. Eck JC, Hodges SD, Humphreys SC. Whiplash: a review of a commonly misunderstood injury. Am J Med. 2001;110(8):651–6.
5. Freeman MD, Croft AC, Rossignol AM, Weaver DS, Reiser M. A review and methodologic critique of the literature refuting whiplash syndrome. Spine (Phila Pa 1976). 1999;24(1):86–96.
6. Windsor RE, Gest TR. Cervical Spine Anatomy. Emedicine.medscape.com [Internet]. 2017;1–9. Available from: emedicine.medscape.com/article/1948797-print
7. Nachemson A. The influence of spinal movements on the lumbar intradiscal pressure and on the tensile stresses in the annulus fibrosus. Acta Orthop Scand. 1963;33:183–207.
8. Steilen D, Hauser R, Woldin B, Sawyer S. Chronic Neck Pain: Making the Connection Between Capsular Ligament Laxity and Cervical Instability. Open Orthop J. 2014;8(1):326–45.
9. Spitzer WO. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining" whiplash" and its management. Spine (Phila Pa 1976). 1995;20:1S-73S.
10. Bannister G, Amirfeyz R, Kelley S, Gargan M. Whiplash injury. J Bone Joint Surg Br. 2009;91(7):845–50.
11. Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Giani C, Zbinden AM, Radanov BP. Central hypersensitivity in chronic pain after whiplash injury. Clin J Pain. 2001;17(4):306–15.
12. Tameem A, Kapur S, Mutagi H. Whiplash injury. Contin Educ Anaesth Crit Care Pain. 2014 Aug;14(4):167–70.
13. Rodriquez AA, Barr KP, Burns SP. Whiplash: pathophysiology, diagnosis, treatment, and prognosis. Muscle Nerve Off J Am Assoc Electrodiagn Med. 2004;29(6):768–81.

14. Cooper G, Bailey B, Bogduk N. Cervical zygapophysial joint pain maps. Pain Med. 2007;8(4):344–53.

15. Bogduk N, Govind J. Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment. Lancet Neurol [Internet]. 2009;8(10):959–68. Available from: http://dx.doi.org/10.1016/S1474-4422(09)70209-1

16. Aprill C, Axinn MJ, Bogduk N. Occipital headaches stemming from the lateral atlanto-axial (C1-2) joint. Cephalalgia. 2002;22(1):15–22.

17. Choi I, Jeon SR. Neuralgias of the head: occipital neuralgia. J Korean Med Sci. 2016;31(4):479–88.

18. Lee C, Son B. Decompression of the greater occipital nerve for persistent headache attributed to whiplash accompanying referred facial trigeminal pain. World Neurosurg. 2021;155:e814–23.

19. Lewis LM, Docherty M, Ruoff BE, Fortney JP, Keltner RA. Flexion-extension views in the evaluation of cervical-spine injuries. Ann Emerg Med. 1991;20(2):117–21.

20. Jónsson HJ, Bring G, Rauschning W, Sahlstedt B. Hidden cervical spine injuries in traffic accident victims with skull fractures. J Spinal Disord. 1991 Sep;4(3):251–63.

21. White AA, Johnson RM, Panjabi MM, Southwick WO. Biomechanical analysis of clinical stability in the cervical spine.pdf. Clin Orthop Relat Res. 1976;No. 109(109):85–96.

22. Kim CW, Perry A, Garfin SR. Spinal instability: The orthopedic approach. Semin Musculoskelet Radiol. 2005;9(1):77–87.

23. Knopp R, Parker J, Tashjian J, Ganz W. Defining radiographic criteria for flexion-extension studies of the cervical spine. Ann Emerg Med. 2001;38(1):31–5.

24. Róbert, Veress. Kandidátusi Értekezés A dens axis törések korai, korszerű kezelése. 1993.

25. Hino H, Abumi K, Kanayama M, Kaneda K. Dynamic motion analysis of normal and unstable cervical spines using cineradiography. An in vivo study. Spine (Phila Pa 1976). 1999 Jan;24(2):163–8.

26. NSW State Insurance Regulatory Authority. Guidelines for the management of acute whiplash - associated disorders - for health professionals [Internet]. NSW State Insurance Regulatory Authority. 2014. Available from: https://www.sira.nsw.gov.au/resources-library/motor-accident-resources/publications/for-professionals/whiplash-resources/SIRA08104-Whiplash-Guidelines-1117-396479.pdf

27. Verhagen AP, Scholten-Peeters GGGM, Van Wijngaarden S, De Bie RA, Bierma-Zeinstra SMA. Conservative treatments for whiplash. Cochrane Database Syst Rev. 2007;(2).

28. Barnsley L, Bogduk N. Medial Branch Blocks Are Specific for the Diagnosis of Cervical Zygapophyseal Joint Pain. Reg Anesth. 1993;18:343–50.

29. Barnsley L, Lord S, B Wallis NB. The Prevlence of Chronic Cervical Zygapophysial Joint Pain After Whiplash. Spine (Phila Pa 1976). 1995;20(1):20–6.

30. Lord SM, McDonald GJ, Bogduk N. Percutaneous radiofrequency neurotomy of the cervical medial branches: A validated treatment for cervical zygapophysial joint pain. Vol. 8, Neurosurgery Quarterly. 1998. p. 288–308.

31. Finlayson RJ, Etheridge JPB, Tiyaprasertkul W, Nelems B, Tran DQH. A randomized comparison between ultrasound- and fluoroscopy-guided C7 medial branch block. Reg Anesth Pain Med. 2015;40(1):52–7.

32. Finlayson RJ, Etheridge JPB, Vieira L, Gupta G, Tran DQH. A randomized comparison between ultrasound- and fluoroscopy-guided third occipital nerve block. Reg Anesth Pain Med. 2013;38(3):212–7.

33. Finlayson RJ, Gupta G, Alhujairi M, Dugani S, Tran DQHH. Cervical medial branch block: A novel technique using ultrasound guidance. Reg Anesth Pain Med. 2012;37(2):219–23.

34. Eichenberger U, Greher M, Kapral S, Marhofer P, Wiest R, Remonda L, et al. Sonographic Visualization and Ultrasound-guided Block of the Third Occipital Nerve Prospective for a New Method to Diagnose C2–C3 Zygapophysial Joint Pain. Anesthesiology. 2006;104(2):303–8.

35. Siegenthaler A, Schliessbach J, Curatolo M, Eichenberger U. Ultrasound anatomy of the nerves supplying the cervical zygapophyseal joints: An exploratory study. Reg Anesth Pain Med. 2011;36(6):606–10.

36. Siegenthaler A, Narouze S, Eichenberger U. Ultrasound-guided third occipital nerve and cervical medial branch nerve blocks. Tech Reg Anesth Pain Manag [Internet]. 2009;13(3):128–32. Available from: http://dx.doi.org/10.1053/j.trap.2009.06.003

37. Siegenthaler A, Mlekusch S, Trelle S, Schliessbach J, Curatolo M, Eichenberger U. Accuracy of ultrasound-guided nerve blocks of the cervical zygapophysial joints. Anesthesiology. 2012;117(2):347–52.

38. Beckman WA, Mendez RJ, Paine GF, Mazzilli MA. Cerebellar Herniation After Cervical Transforaminal Epidural Injection. Reg Anesth Pain Med. 2006;31(3):282–5.

39. Bogduk N, Dreyfuss P, Baker R, Yin W, Landers M, Hammer M, et al. Complications of spinal diagnostic and treatment procedures. Pain Med. 2008;9(SUPPL. 1).

40. Ma DJ, Gilula LA, Riew KD. Complications of fluoroscopically guided extraforaminal cervical nerve blocks: An analysis of 1036 injections. J Bone Jt Surg - Ser A. 2005;87(5):1025–30.

41. Malhotra G, Abbasi A, Rhee M. Complications of transforaminal cervical epidural steroid injections. Spine (Phila Pa 1976). 2009;34(7):731–9.

42. Ludwig MA, Burns SP. Spinal cord infarction following cervical transforaminal epidural injection: a case report. Spine (Phila Pa 1976). 2005;30(10):266–8.

43. Park D, Seong MY, Kim HY, Ryu JS. Spinal cord injury during ultrasound-guided C7 cervical medial branch block. Am J Phys Med Rehabil. 2017;96(6):e111–4.

44. Hauser R, Medical C, Medicine R. Dextrose Prolotherapy For Unresolved Neck Pain An observational study of patients with unresolved neck pain who were treated with dextrose prolotherapy at an outpatient charity cli... 2016;(January).

45. Hooper RA, Frizzell JB, Faris P. Case series on chronic whiplash related neck pain treated with intraarticular zygapophysial joint regeneration injection therapy. Pain Physician. 2007;10(2):313–8.

46. Jeszenszky D, Fekete TF, Lattig F, Bognár L. Intraarticular atlantooccipital fusion for the treatment of traumatic occipitocervical dislocation in a child: A new technique for selective stabilization with nine years follow-up. Spine (Phila Pa 1976). 2010;35(10):421–6.

47. Jeszenszky D, Fekete T, Kleinstück F, Haschtmann D, Loibl M. Transoral closed reduction of fixed Atlanto-Axial Rotatory-Subluxation (AARS) in childhood and adolescence. Clin Spine Surg. 2018;31(5):E252–6.

48. Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): Part 5 - Surgical and injection-based interventions for chronic WAD. Pain Res Manag. 2010;15(5):323–34.

49. Zhou L, Kambin P, Casey KF, Bonner FJ, O'Brien E, Shao Z, et al. Mechanism research of cryoanalgesia. Neurol Res. 1995;17(4):307–11.

50. Law L, Rayi A, Derian A. Cryoanalgesia. 2018;

51. Alves R, Grimalt R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. Ski Appendage Disord. 2018;4(1):18–24.

52. DeChellis DM, Cortazzo MH. Regenerative medicine in the field of pain medicine:

Prolotherapy, platelet-rich plasma therapy, and stem cell therapy-Theory and evidence. Tech Reg Anesth Pain Manag [Internet]. 2011;15(2):74–80. Available from: http://dx.doi.org/10.1053/j.trap.2011.05.002

53. Harmon KG. Muscle injuries and PRP : what does the science say ? 2010;44(9):17–9.

54. Schie HTM Van, Weinans H, Verhaar JAN. Can Platelet-Rich Plasma Enhance Tendon Repair ? 2008;1171–8.

55. Kurosaka M. In Vitro and Its In Vivo Application with Biodegradable. 2007;13(5).

56. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Prim Care Clin Off Pract. 2010;37(1):65–80.

57. Alfredson H, Öhberg L. Neovascularisation in chronic painful patellar tendinosis—promising results after sclerosing neovessels outside the tendon challenge the need for surgery. Knee surgery, Sport Traumatol Arthrosc. 2005;13:74–80.

58. Distel LM, Best TM. Prolotherapy: a clinical review of its role in treating chronic musculoskeletal pain. PM R. 2011;3:S78-81.

59. Jensen KT, Rabago DP, Best TM, Patterson JJ, Vanderby Jr R. Response of knee ligaments to prolotherapy in a rat injury model. Am J Sports Med. 2008;36(7):1347–57.

60. Hung C-Y, Hsiao M-Y, Ke-Vin C, Han D-S, Wang TG. Comparative effectiveness of dextrose prolotherapy versus control injections and exercise in the management of osteoarthritis pain: a systematic review and meta-analysis. J Pain Res. 2016;9:847–57.

61. Bae G, Kim S, Lee S, Lee WY, Lim Y. Prolotherapy for the patients with chronic musculoskeletal pain: systematic review and meta-analysis. Anesth Pain Med. 2021;16(1):81–95.

62. Hauser RA, Lackner JB, Steilen-Matias D, Harris DK. A systematic review of dextrose prolotherapy for chronic musculoskeletal pain. Clin Med Insights Arthritis Musculoskelet Disord. 2016;9:139–59.

63. Fairbank JC, Pynsent PB. The oswestry disability index. Spine (Phila Pa 1976). 2000;25(22):2940–53.

64. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.

65. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. Med Care. 2008;46(3):266–74.

66. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. Pain Med. 2005;6(6):432–42.

67. Langford DJ, Tauben DJ, Sturgeon JA, Godfrey DS, Sullivan MD, Doorenbos AZ. Treat the Patient, Not the Pain: Using a Multidimensional Assessment Tool to Facilitate Patient-Centered Chronic Pain Care. J Gen Intern Med. 2018;33(8):1235–8.

68. Dorman T. Whiplash Injuries, Treatment with Prolotherapy and a New Hypothesis. J Orthop Med. 1999;21(1):13–21.

69. Hackett G, Hemwall G, Montgomery G. Ligament and tendon relaxation treated by prolotherapy. [Internet]. 5th ed. Madison WI: Hackett Hemwall Patterson Foundation. 1993. Available from: http://hhpfoundation.org/

70. Garrett M, Consiglieri G, Kakarla UK, Chang SW, Dickman CA. Occipitoatlantal dislocation. Neurosurgery. 2010;66(SUPPL. 3):48–55.

71. Mead LB, Millhouse PW, Krystal J, Vaccaro AR. C1 fractures: a review of diagnoses, management options, and outcomes. Curr Rev Musculoskelet Med [Internet]. 2016;9(3):255–62. Available from: http://dx.doi.org/10.1007/s12178-016-9356-5

72. Finlayson RJ, Etheridge JPB, Tiyaprasertkul W, Nelems B, Tran DQH. A prospective validation of biplanar ultrasound imaging for C5-C6 cervical medial branch blocks. Reg Anesth Pain Med. 2014;39(2):160–3.

73. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet [Internet]. 2010;376(9754):1751–67. Available from: http://dx.doi.org/10.1016/S0140-6736(10)61160-9

74. McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis a randomized clinical trial. JAMA - J Am Med Assoc. 2017;317(19):1967–75.

75. Stogicza AR, Guo MYF, Rabago D. Whiplash injury successfully treated with prolotherapy: A case report with long-term follow up. Regen Med. 2020;15(9):2075–84.

76. Igwe N, Patel NC, Aijaz T. Regenerative Therapy In Pain. In: StatPearls [Internet]. StatPearls Publishing; 2022.

77. Rabago D, Yelland M, Patterson J, Zgierska A. Prolotherapy for chronic musculoskeletal pain. Vol. 84, American family physician. United States; 2011. p. 1208–10.

78. Banks AR. A Rationale for prolotherapy. J Orthop Med. 1991;13(3):54–9.

79. Johnston E, Andrali SS, Kochan A, Johnston M, Lovick J. Prolotherapy-Induced Cartilage Regeneration : Investigating Cellular-Level Mechanisms of Action with Mouse Preosteoblast Cells. JSM Biochem Mol Biol. 2017;4(310):1032.

80. Ylärinne JH, Qu C, Lammi MJ. Hypertonic conditions enhance cartilage formation in scaffold-free primary chondrocyte cultures. Cell Tissue Res. 2014;358(2):541–50.

81. Linetsky F, Botwin K, Gorfin L, Al. E. Regeneration injection therapy (RIT): Effectiveness and appropriate usage. [Internet]. Fla Acad Pain Med. 2001. Available from: http://www.gracermedicalgroup.com/resources/articles/rf

82. Hassan F, Trebinjac S, Murrell WD, Maffulli N. The effectiveness of prolotherapy in treating knee osteoarthritis in adults: A systematic review. Br Med Bull. 2017;122(1):91–108.

83. Rabago D, Best TM, Beamsley M, Patterson J. A systematic review of prolotherapy for chronic musculoskeletal pain. Clin J Sport Med. 2005;15(5):376–80.

84. Rabago D, Mundt M, Zgierska A, Grettie J. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. Complement Ther Med. 2015;

85. Sit RWWS, Chung VCHC, Reeves KD, Rabago D, Chan KKWK, Chan DCCC, et al. Hypertonic dextrose injections (prolotherapy) in the treatment of symptomatic knee osteoarthritis: A systematic review and meta-analysis. Sci Rep [Internet]. 2016;6(April):1–11. Available from: http://dx.doi.org/10.1038/srep45879

86. Arias-Vázquez PI, Castillo-Avila RG, Tovilla-Zárate CA, Quezada-González HR, Arcila-Novelo R, Loeza-Magaña P. Efficacy of prolotherapy in pain control and function improvement in individuals with lateral epicondylitis: a systematic review and meta-analysis. ARP Rheumatol. 2022;1(2):152–67.

87. Anil U, Markus DH, Hurley ET, Manjunath AK, Alaia MJ, Campbell KA, et al. The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. Knee [Internet]. 2021 Oct 1 [cited 2023 Dec 31];32:173–82. Available from: https://doi.org/10.1016/j.knee.2021.08.008

88. Bansal H, Leon J, Pont JL, Wilson DA, Bansal A, Agarwal D, et al. Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy. Sci Rep [Internet]. 2021;11(1):1–10. Available from: https://doi.org/10.1038/s41598-021-83025-2

89. Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of

Randomized Controlled Trials. Cartilage. 2021;13(1):364S-375S.

90. Le ADK, Enweze L, DeBaun MR, Dragoo JL. Current Clinical Recommendations for Use of Platelet-Rich Plasma. Curr Rev Musculoskelet Med. 2018;11(4):624–34.

91. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, Harrison JR, Gribbin CK, LaSalle EE, et al. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study. PM R. 2016;8(1):1–10.

92. Pettine KA, Murphy MB, Suzuki RK, Sand TT. Percutaneous injection of autologous bone marrow concentrate cells significantly reduces lumbar discogenic pain through 12 months. Stem Cells. 2015;33(1):146–56.

93. Wu J, Zhou J, Liu C, Zhang J, Xiong W, Lv Y, et al. Prospective Study Comparing Platelet-Rich Plasma and LA/Corticosteroid in Intra-Articular Injection for the Treatment of L umbar Facet Joint Syndrome. Pain Pract. 2017;17(7):914–24.

94. Wu J, Du Z, Lv Y, Zhang J, Xiong W, Wang R, et al. A new technique for the treatment of lumbar facet joint syndrome using intra-articular injection with autologous platelet rich plasma. Pain Physician. 2016;19(8):617–25.

95. Allen Hooper R, Yelland M, Fonstad P, Southern D. Prospective case series of litigants and non-litigants with chronic spinal pain treated with dextrose prolotherapy. Int Musculoskelet Med. 2011;33(1):15–20.

96. Dechow E, Davies RK, Carr AJ, Thompson PW. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. Rheumatology (Oxford). 1999 Dec;38(12):1255–9.

97. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27(3):158–67.

98. Hauser, Ross A.; Hauser, Marion A; Halian P. Dextrose Prolotherapy for Unresolved Neck Pain. Pract Pain Manag. 2007;10(0):56–69.

99. Centeno CJ, Elliott J, Elkins WL, Freeman M. Fluoroscopically guided cervical prolotherapy for instability with blinded pre and post radiographic reading. Pain Physician. 2005;8(1):67–72.

100. Allison DJ, Ebrahimzadeh S, Muise S, Joseph S, Roa Agudelo A, Lawson A, et al. Intra-articular corticosteroid injections versus platelet-rich plasma as a treatment for cervical facetogenic pain: a randomized clinical trial. Reg Anesth Pain Med. 2024 Nov;

101. Straum OK. The optimal platelet concentration in platelet-rich plasma for proliferation of human cells in vitro-diversity, biases, and possible basic experimental principles for further research in the field: A review. PeerJ. 2020;8.

102. Smith A, Andruski B, Deng G, Burnham R. Interventional Pain Medicine Cervical facet joint platelet-rich plasma in people with chronic whiplash-associated disorders : A prospective case series of longer term 6- and 12- month outcomes. Interv Pain Med [Internet]. 2023;2(1):100237. Available from: https://doi.org/10.1016/j.inpm.2023.100237

103. Atluri S, Murphy MB, Dregalla R, Herrera J, Boachie-Adjei K, Bhati SVivek Manocha V, Navneet Boddu, Pavan Yerramsetty, Zaid Syed, Meghana Ganjam, Divit Jain, Zaynab Syed, Nikhil Grandhi and LM. Evaluation of the Effectiveness of Autologous Bone Marrow Mesenchymal Stem Cells in the Treatment of Chronic Low Back Pain Due to Severe Lumbar Spinal Degeneration. Pain Physician. 2022;193–207.

104. Kirchner F, Anitua E. Intradiscal and intra articular facet infiltrations with plasma rich in growth factors reduce pain in patients with chronic low back pain. J Craniovertebr Junction Spine. 2016;7(4):250.

105. Kirchner F, Milani I, Martinez A, Kirchner-Bossi N, Prado R, Padilla S, et al. Plasma Rich in Growth Factors (PRGF) in the Treatment of Cervical and Lumbar Back Pain: A Retrospective Observational Clinical Study. Pain Physician. 2021 Aug;24(5):E649–60.

106. Cohen SP, Lee Peterlin B, Fulton L, Neely ET, Kurihara C, Gupta A, et al. Randomized, double-blind, comparative-effectiveness study comparing pulsed radiofrequency to steroid injections for occipital neuralgia or migraine with occipital nerve tenderness. Pain. 2015;156(12):2585–94.

107. Kim CH, Hu W, Gao J, Dragan K, Whealton T, Julian C. Cryoablation for the treatment of occipital neuralgia. Pain Physician. 2015;18(3):E363–8.

108. Stechison MT, Mullin BB. Surgical treatment of greater occipital neuralgia: An appraisal of strategies. Acta Neurochir (Wien). 1994;131(3–4):236–40.

109. Vanderhoek MD, Hoang HT, Goff B. Ultrasound-Guided Greater Occipital Nerve Blocks and Pulsed Radiofre- quency Ablation for Diagnosis and Treatment of Occipital Neuralgia. 2013;3(2):3–6.

110. Vanelderen P, Rouwette ÞT, Vooght P De, Puylaert M, Vissers K, Zundert J Van. Pulsed Radiofrequency for the Treatment of Occipital Neuralgia A Prospective Study With 6 Months of Follow-Up. 2010;35(2):148–51.

111. Gille O, Lavignolle B, Vital JM. Surgical Treatment of Greater Occipital Neuralgia by Neurolysis of the Greater Occipital Nerve and Sectioning of the Inferior Oblique Muscle. Spine (Phila Pa 1976). 2004;29(7):828–32.

112. Emal Wahezi S, Wahezi SE, Silva K, Shaparin N, Lederman A, Emam M, et al. Currently recommended TON injectate volumes concomitantly block the GON:

Clinical implications for managing cervicogenic headache. Pain Physician [Internet]. 2016;19:E1079–86. Available from: www.painphysicianjournal.com

113. Greher M, Moriggl B, Curatolo M, Kirchmair L, Eichenberger U. Sonographic visualization and ultrasound-guided blockade of the greater occipital nerve: A comparison of two selective techniques confirmed by anatomical dissection. Br J Anaesth. 2010;104(5):637–42.

114. Tubbs RS, Salter EG, Wellons JC, Blount JP, Oakes WJ. Landmarks for the identification of the cutaneous nerves of the occiput and nuchal regions. Clin Anat. 2007;20(3):235–8.

115. Narouze SN, Provenzano DA, Vydyanathan A, Park KD, Lim D, Lee WY, et al. Sonographically guided cervical facet nerve and joint injections. J Ultrasound Med. 2013;32(11):1885–96.

116. Kweon T, Kim J, Lee H, Kim M, Lee YW. Anatomical analysis of medial branches of dorsal rami of cervical nerves for radiofrequency thermocoagulation. Reg Anesth Pain Med. 2014;39(6):465–71.

117. Wahezi SE, Molina JJ, Alexeev E, Georgy JS, Haramati N, Erosa SA, et al. Cervical Medial Branch Block Volume Dependent Dispersion Patterns as a Predictor for Ablation Success: A Cadaveric Study. PM R. 2019;11(6):631–9.

118. Lee SH, Kang CH, Lee SH, Derby R, Yang SN, Lee JE, et al. Ultrasound-guided radiofrequency neurotomy in cervical spine: sonoanatomic study of a new technique in cadavers. Clin Radiol [Internet]. 2008;63(11):1205–12. Available from: http://dx.doi.org/10.1016/j.crad.2008.06.001

9 Bibliography

Bibliography related to this thesis

1 Journal article	Galand E, ChangChien G, Trescot AMT, Stogicza A. Regenerative Medicine Techniques in the Management of Chronic Tendinopathy. Techniques in Regional Anesthesia and Pain Management
2 Journal article	Stogicza A, Trescot A, Rabago D. Pain Pract. 2019 Mar 1. doi: 10.1111/papr.12779. New Technique for Cryoneuroablation of the Proximal Greater Occipital Nerve.
3 Journal article	Stogicza A, Guo MY, Rabago D. Whiplash injury successfully treated with prolotherapy: a case report with long-term follow up. Regenerative Medicine. Regen Med. 2020 Sep;15(9):2075-2084. doi: 10.2217/rme-2020-0063.
4 Journal article	Stogicza AR, Berkman A, Mansano AM, Frederico TN, Reddy R, Oliveira C, Chen WC, Declerck C, Lam S, Sommer M, Racz E, Assis FD, Trescot AM, Ares JA, Del Rey MLP, van Kuijk S. A Comparison of Precision and Safety using Three Recognized Ultrasound-Guided Approaches to Cervical Medial Branch Blocks: A Cadaver Study. Pain Physician. 2024 Jan;27(1):E157-E168. PMID: 38285047.
5 Journal article	Barbieri M, Colombini A, Stogicza A, de Girolamo L. Effectiveness of plasma rich in growth factors in the management of chronic spinal pain: a case series of 32 patients. Regen Med. 2022 Mar;17(3):175-184. DOI: 10.2217/rme-2021-0128

Complete Personal bibliography

6 Journal article	Lollo L, Bhananker S, Stogicza A. Postoperative sciatic and femoral or saphenous nerve blockade for lower extremity surgery in anesthetized adults. Int J Crit Illn Inj Sci. 2015 Oct-Dec;5(4):232-6. doi: 10.4103/2229-5151.170846. PMID: 26807391; PMCID: PMC4705568. 10.4103/2229-5151.170846
7 Journal article	Gordon DB1, Loeser JD, Tauben D, Rue T, Stogicza A, Doorenbos A. Development of the KnowPain-12 pain management knowledge survey. Clin J Pain. 2014 Jun;30(6):521-7. Doi: 10.1097/AJP.0000000000000016
8 Journal article	De Pinto M, Dagal A, O'Donnel Brendan, Stogicza A, Chiu S, Edward WT. Regional anesthesia for management of acute pain in the intensive care unit. Int J Crit illn Scie 2015 Jul-Sep 5(3): 138-143 Doi: 10.4103/2229-5151.164917
9	Stogicza AR, Peng P. Cryoanalgesia for shoulder pain: a motor-sparing approach to rotator cuff disease. Reg Anesth Pain Med 2022; 0:1–5. doi:10.1136/rapm-2022-103670

10	Lo Bianco G , Misseri G, Stogicza AR, Cesare G, Li S , Day M, Kennedy DJ, Schatman ME . Radiofrequency Ablation for Chronic Lumbar Zygapophyseal Joint Pain Using a V-Shaped Active Tip Needle: An Observational Retrospective Study. Journal of Pain Research. 2023:16 Pages 1243—1255 10.2147/JPR.S406714
11	Lo Bianco G, Tinnirello A, Papa A, Torrano V, Russo G, Stogicza A, Mercadante S, Cortegiani A, Mazzoleni S, Schatman ME. Interventional Pain Procedures: A Narrative Review Focusing on Safety and Complications. Part 1 Injections for Spinal Pain. J Pain Res. 2023 May 18;16:1637-1646. doi: 10.2147/JPR.S402798. PMID: 37223436; PMCID: PMC10202209.

10 Acknowledgements

I would like to express my heartfelt gratitude to several individuals who have been instrumental in my journey. First, to my first mentor, Dr. Edit Rácz, for introducing me to the fascinating world of anesthesia and pain medicine. To Professor Andrea Trescot, whose unwavering support since our time together at the University of Washington has been invaluable, and for showing me the transformative potential of regenerative medicine over 20 years ago. To Professor Philip Peng, whose guidance in the publishing process has greatly contributed to my growth. To Professor Lóránd Erőss, for his continued support throughout my PhD work. To Dr. László Entz, for providing constructive feedback on my thesis. To my family, for their patience, understanding and tolerating the long workhours throughout my career. And last, but certainly not least, to my many patients, without whom I would not have gained the invaluable experience I have today.