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Lumbar facet joint radiofrequency denervation therapy for recurrent chronic low back pain: enhanced outcome compared with chemical neurolysis (ethyl alcohol 95% or glycerol 20%)

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1. Introduction

1.1 Motivation and objective

Chronic pain is responsible for the highest number of years lived with disability of all chronic medical conditions [1,2].As it is the most expensive cause of work-related disability, it has significant direct and indirect financial consequences [3-5].Among these chronic pain patients, chronic low back pain (CLBP) is a significant contributor to morbidity and disability[5].Facet syndrome is a commonly accepted cause of CLBP [6-8].As CLBP is a broad complaint resulting from a variety of underlying problems of varying severity [9], the diagnostic process is challenging.

CLBP, including lumbar facetogenic chronic back pain, can be treated with a variety of therapies and medical interventions that can complement each other. For instance, behavioural therapy is often used in combination with established physical exercises to reduce disability by addressing maladaptive pain behaviours and cognitive processes, as they have proven to be effective in treating CLBP [10-14].If conservative treatment fails to relieve symptoms, several minimally invasive treatment modalities have been used to manage recurrent lumbar facet joint pain. These include radiofrequency denervation (RFD) and chemical neurolysis with ethyl alcohol (50%-100%), phenol (5%-10%), or glycerol (20%-100%) [15-26].

Comparative studies on the medium- and long-term treatment of chronic facet joint arthropathy are limited, and success rates and complications remain unknown. The level of evidence supporting the success of therapeutic nerve blocks is currently between level II-1 and II-2 with a 1B or C/strong recommendation. As for alternative invasive therapeutic options (e.g. RFD), the evidence is II-2 to II-3 with a recommendation of 1B or 1C [8,27-29].

With this in mind, this study aims to compare the effects of RFD and chemical neurolysis using either ethyl alcohol 95% or glycerol 20%. The study also seeks to determine the short-term and medium-term clinical outcomes of the different types of neurolysis.

1.2 Problem statement

Chronic low back pain (CLBP) is a complex condition with great heterogeneity and is often multifactorial. Experimental studies suggest that in most patients, the pain originates from the facet joint capsule, which is highly innervated by both high-threshold nociceptive and autonomic nerve fibers [30,31].Lumbar facetogenic pain is a common cause of low back pain, although diagnosis can be challenging due to the absence of radiographic findings. However, effective diagnostic blocks can confirm the presence of isolated facetogenic pain [6-8].

It is a challenge when it comes to the recurrence of facet joint pain after successful medial branch blocks or intra-articular blocks with steroids, especially in patients with cardiac implantable electronic devices (CIEDs). Spine specialists often encounter the issue of pain recurrence following initial or repeated radiofrequency denervation treatment of the medial branch of the posterior ramus. This prompts the search for alternative ablation methods that offer longer-lasting pain relief.

Radiofrequency denervation (RFD) is a physical technique used to relieve spinal pain by modulating the neural transmission of nociceptive stimuli. It deactivates nerve fibers that contribute to pain perception and transmission by applying a local cellular electrical current and high local temperatures to inactivate sensory nerves through heat denaturing, thus preventing the transmission of nociceptive impulses [32] . There is moderate to strong evidence that RFD provides both short- and longer-term relief of low back pain originating in the facet joints [33]. The use of chemical neurolysis for treating low back pain with varying concentrations of ethyl alcohol, phenol or glycerol is a controversial topic [34].However, it may be considered as a solution and alternative for RFD, provided that safety is ensured.

In order to clarify the role of chemical neurolysis, a prospective cohort study of adult patients with recurrent chronic low back pain who did not respond to non-invasive therapy and steroid injections will be conducted. The study will enrol patients between 1 December 2017 and 1 December 2019.These patients will undergo spinal imaging to exclude alternative diagnoses. The patients will then be divided into groups according to their treatment modality. The study will compare three groups: radiofrequency denervation (Gr. RFD), chemical neurolysis with Ethyl-Alcohol 95% (Gr. EA-95), and Glycerol 20% (Gr. Gly-20). The study will use the Visual Analogue Scale (VAS) and the Core Outcome Measures Index for the Back (COMI-back) to measure outcome parameters at different time points during the study. VAS assesses pain levels[35], and COMI-back is a brief and validated instrument for assessing the main outcomes in patients with back problems, including pain, function, symptom-related well-being, quality of life, and overall disability [36]. Additionally, complications are to be documented and compared between groups. The outcome will be determined pre-intervention, after 6 weeks, and at 6 and 12 months.

1.3 Structure of the dissertation

The structure and content of the dissertation are described below.

Section 1 begins with a description of the motivation and objectives, the problem definition and the approach to the topic. This is followed in Section 2 by an introduction to the theoretical basis and definitions of pain, chronic low back pain (CLBP), lumbar facetogenic CLBP, diagnostics, and therapies and treatment modalities for CLBP. Additionally, this section includes publications related to CLBP, lumbar facetogenic chronic back pain and

various invasive treatment modalities. Based on these publications, the research gap is identified.

Section 3 specifies the research question and study hypothesis of the thesis, taking into account the identified research gaps.

Section 4 is dedicated to Materials and Methods, beginning with the study design and cohorts. The study involved executing diagnostic medial branch blocks, enrolling and grouping participants, and performing radiofrequency denervation and chemical neurolysis using ethyl alcohol 95% and glycerol 20%. The statistical methods are finally presented at the end of this section.

Section 5 summarises the study results, followed by a discussion of their implications for future research on treatment options for lumbar facetogenic chronic back pain in Section 6. Additionally in Section 6, the study's limitations are addressed.

2. Background of Pain and Chronic Low Back Pain

2.1 Pain

2.1.1. Definition of pain

The International Association for the Study of Pain (IASP) describes pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [37]. This novel definition replaces the former IASP definition of pain which was adopted back in 1979: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [37]. The old IASP definition of pain has been utilized globally and was well accepted in both the scientific and clinical field. Increased understanding of the pathophysiological background of pain from both clinical and experimental research, recognition of global cultural/linguistic differences in pain perception, and new insights into the impact of socio-economic aspects on pain handling formed the impetus for a revision of the traditional IASP definition [38,39]. The novel definition entails minor alterations compared to the previous definition and is based on a precious international and multidisciplinary process involving experts from different backgrounds and patients. The updated definition is believed to better reflect prolonged pain conditions in which pain is experienced, even in the absence of ongoing tissue damage. In addition, the previous version of the definition attributed pain without an identifiable physical cause mainly to psychological problems rather than to a well-described dysfunction of the neurological system. This has been changed in the novel to a more integral definition of pain by the IASP in 2020 [38]. Furthermore, according to both the previous and the current IASP definitions still consider pain to be a phenomenon resulting from the interplay between sensory and emotional experiences [37,38,40].If pain occurs for a prolonged period of time, the condition may be classified as a chronic pain syndrome or chronic pain disease. This type of pain persists despite the absence of an actual pain stimulus. Traditionally, the distinction between acute and chronic pain is based on a subjective time interval between the occurrence and disappearance of the pain. Chronic pain persists longer than anticipated and exceeds the normal recovery time after the induction of the pain stimulus [41]. The two most commonly used purely temporal cut-off values in the literature are three and six months since the onset of pain, respectively [42]. Alternatively, some have set the transition from acute to chronic pain at 12 months [43]. In contrast to pain, which is mainly considered as a symptom of an underlying pathology, the condition of chronic pain has been integrated in the latest version of the International Classification of Diseases version 11 (ICD-11) [44]. In the ICD-11, chronic pain is an overlapping entity for seven subtypes of further specific chronic pain conditions: (1) chronic primary pain; (2) chronic cancer-related pain; (3) chronic postsurgical

or post-traumatic pain; (4) chronic neuropathic pain; (5) chronic secondary headache or orofacial pain; (6) chronic secondary visceral pain; and (7) chronic secondary musculoskeletal pain. With the exception of the chronic primary pain subtype (such as fibromyalgia), all other pain conditions are secondary to an underlying disease which persists for more than 3 months and requires special medical treatment[44]. The previously mentioned classification system for chronic pain was developed by an international task force with members from the World Health Organization and the IASP. The goal of the novel system is to support world-wide standardization of definitions for chronic pain in different settings: e.g. in primary care, specialized pain medicine and also in low-resource areas [44].

2.1.2. Types of pain

Patients may experience different types of pain, each with its specific clinical characteristics and pathophysiology. Consequently, different therapeutic approaches are required to treat these distinct types of pain. In general, three different categories of pain are distinguished: (i) nociceptive pain, (ii) neuropathic pain, and (iii) nociplastic pain. The latter category is relatively recent and the mechanisms of this type of pain are still poorly understood. In brief, nociceptive pain results from inflammation and subsequent tissue damage, whereas neuropathic pain arises from damaged nerves. It is believed that nociplastic pain is associated with inadequate sensory processing and pain modulation within the central nervous system. Nociplastic pain can occur either as an isolated pain type or in combination with nociceptive and/or neuropathic pain. It is of great importance to distinguish between these different pain categories because it has significant therapeutic consequences. Given the well-known key differences in pathophysiology, natural course, and the impact of interventions on pain perception, different treatment protocols are applied to the different categories. The three different categories of (chronic) pain are described in more detail below.

I. Nociceptive pain

Nociceptive pain follows the stimulation of nociceptors by a noxious stimulus in peripheral nerves (Aδ and C fibers). Nociceptors are a subset of sensory neurons with the key task of identifying potential danger or damage to an organism, making them of utmost relevance for the survival of organisms. Nociceptors are free nerve endings and are mostly polymodal, which allows them to respond to multiple stimuli. Different types of stimuli have been described: mechanical stimuli (such as local pressure, squeezing, tearing, and cutting of tissue), thermal stimuli (heat or cold) and chemical stimuli (such as capsaicin in spicy food or heat patches) [45]. These stimuli trigger the transduction of the stimulus into a sensory potential at the level of the sensor molecules in the sensory endings of the nociceptors. When the sensory potential reaches or exceeds a specific threshold, an action potential gets triggered. Action potentials are conducted to the dorsal horn and further along axons [46-48].

Nociceptive signals have the potency to get transmitted to the brain, but prompt redirection of signals by spinal reflex loops may also occur to evoke instant muscle reflexes to prevent further damage [49,50]. There are also so-called ´silent nociceptors´ or mechanically insensitive afferents (MIAs), which are not excitable in tissue under physiological conditions. However, in the context of inflammation, they become sensitive to pain stimuli by lowering the stimulus threshold [51,52].The great importance of nociceptive pain sensation for the survival of organisms is demonstrated by studies on conditions associated with impaired pain sensitivity, such as SCN9A-mutations. SCN9A-encoding is a key element in the proper functioning of the voltage-gated sodium channel Nav1.7, and mutations of the SCN9A-gene are therefore associated with a marked reduction of life expectancy [53].

II. Neuropathic pain

Neuropathic pain is described as pain resulting from a lesion or disease of the somatosensory system. The somatosensory system begins with nerves that transmit signals to the brain via the spinal cord [54,55]. There are two subtypes of neuropathic pain: peripheral and central pain[56].Central neuropathic pain involves damage of the spinal cord or the brain, mainly following cerebrovascular disease like stroke or neurodegenerative disease such as Parkinson. In contrast, peripheral pain involves peripheral nerves, mainly unmyelinated C-fibers or myelinated A-fibers [54,57,58]. Various causes of neuropathic pain have been identified. Systemic pathologies such as metabolic disorders, inflammatory and auto-immune disorders, as well as drug-associated neuropathies may form the basis for neuropathic pain. Local pathologies such as peripheral neuropathies, damage to the nervous system due to injuries, infection, hereditary neuropathies may also lead to neuropathic pain [56]. Clinically, neuropathic pain is characterized by allodynia, hyperalgesia and paresthesia. In most cases, there is no specific trigger for neuropathic pain, and the onset of pain is spontaneous [59].The IASP criteria for neuropathic pain are: i. A lesion or disease of the somatosensory nervous system is identified as the cause of the pain. ii. Pain is limited to a neuroanatomically plausible distribution of the system. iii. Pain is supported by clinical examination, laboratory findings and/or imaging results [60]. Neurophysiological studies in patients with neuropathic pain display increased activity in somatosensory nerve fibers or alterations in endogenous pain control. These findings provide important insights for pre-clinical research on neuropathic pain and have additional diagnostic value as well [61]. As previously mentioned, neuropathic pain should originate from the nervous system, hence a clear relation between the disease and pain distribution is necessary to confirm the diagnosis. Clinical signs confirming the required neuroanatomical relation with the underlying pathology include: allodynia (pain in the absence of a pain stimulus), hyperalgesia (increase pain sensation to a pain stimulus) and paresthesia (the perception of anomalous sensations to a stimulus) [59,60].

The distribution of pain and related clinical symptoms for neuropathic pain have characteristic topographical patterns, which are relevant diagnostic criteria [60,62].

III. Nociplastic pain

This is the youngest category of pain, having been added to the categorization system relatively recently. Nevertheless, the concept of nociplastic pain has been broadly adopted by the field, and this category of pain has also been implemented in clinical treatment standards worldwide for a plethora of diseases already. The entity of nociplastic pain and its specific criteria actually replace the central sensitization (CS) pain described in 2014, as the novel entity better reflects the different aspects of the specific pain phenotype [63-65].In contrast to the other categories of pain, the pathophysiological background of nociplastic pain is poorly understood [63,66]. Although current insights in its pathophysiology imply that nociplastic pain is associated with impaired and/or enhanced processing of pain stimuli. This may occur at various levels of the peripheral or central nervous system, a concept described by Woolf et al., which also encompasses the process of central sensitization [67]. Aberrant signaling patterns in quantitative sensory testing are not only encountered in the involved pain regions, such as in nociceptive or neuropathic pain, but are more widespread. This strongly suggests CNS involvement [68]. Additionally, non-PNS symptoms such as fatigue, sleeping disorders and cognition problems are profound features of nociplastic pain [66].

Nociplastic pain has been defined by the IASP as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain” [69]. As a consequence, specific treatment protocols are required as the impact of peripherally pain-interventions (drugs, infiltration therapy or surgery) is impaired. The IASP-criteria for nociplastic pain include: i. Report pain of at least three months duration, ii. Report a regional rather than discrete pain distribution, iii. Report pain that cannot entirely be explained by nociceptive or neuropathic mechanisms, iv. Show clinical signs of pain hypersensitivity that are at least present in the region of pain [70].In the case all these criteria are present, patients may be diagnosed with nociplastic pain if there is a concurrent history of local pain hypersensitivity in the affected region. Additional prerequisites for the diagnosis of nociplastic pain include the presence of at least one of the following co-morbidities: hypersensitivity to sound, light, odors or sleep disorders, fatigue or cognitive pathologies [63,70]. Diagnostic tests are currently not available, and diagnosis solely relies on clinical symptoms and pain history. Despite nociplastic pain is defined as a separate pain category, an overlap with other pain types (nociceptive/neuropatic) may occur, and it has been proposed by others that nociplasic pain should be considered as part of the chronic pain continuum [66,71]. This pain continuum represents the sum of the interplay between nociceptive/neuropatic pain and additional nociplastic mechanisms. This is in line with recent findings from literature in which

concurrent presence of multiple pain categories has been described in specific patient groups [72].

2.2 Chronic Low Back Pain (CLBP)

2.2.1. Overview

Chronic low back pain (CLBP) may involve three different types of pain: nociceptive, neuropathic, and nociplastic pain, although overlap is common. There is also overlap in the anatomical localization of CLBP. The lumbar spine has a large number of anatomical structures and the involvement of these specific elements (e.g., soft tissue, vertebrae, disco-ligamental structures, facet joints and neurological as well as vascular structures) may individually or in combination lead to CLBP [73]. Chronic low back pain (CLBP), or lumbago, manifests as unpleasant symptoms localized between the gluteal area and the costal margin. Symptoms commonly include not only pain but also muscle tension or stiffness. In cases of additional radiating pain into one or both legs, a sciatic is likely present and this is called sciatica [74].Another factor that is important in diagnosing CLBP is the duration of symptoms. According to the literature and most current guidelines, low back pain is classified according to its duration as acute (pain lasting less than 6 weeks), sub-chronic (6 to 12 weeks), or chronic (more than 12 weeks) [75].

In the previous edition of the ICD-system (the International Classification of Diseases 10th revision (ICD-10), CLBP is included, although the heterogeneity of chronic back pain is not extensively reflected. Therefore, a new classification system was developed in collaboration with the World Health Organization (WHO)and the IASP. In the updated ICD (Edition-11) catalogue, CLBP is classified as ´chronic primary pain´[44].In order to classify as chronic primary pain, at least one anatomical region should be affected. Pain symptoms should furthermore persist or recur for a time period exceeding three months. Additionally, this pain condition should be associated with emotional or functional impairment and has no relation to any other chronic pain pathology [76]. For patients with back pain suffering from other concurrent painful conditions, such as endometriosis or inflammatory bowel disease, alternative coding is indicated. These patients are coded in the ICD-11 system as ´chronic secondary musculoskeletal pain´[44].

Further subclassifications of low back pain have been described in the literature, and some of these additional subclassifications have also been adopted and implemented in clinical treatment guidelines because of their practical implications. Commonly, patients with CLBP are classified into four categories: i. Patients with proven visceral pathology, ii. Patients with proven *specific* spinal pathology, iii. Patients with radiating pain/radicular syndromes, and iv. those patients with *nonspecific* low back pain [75].Non-specific chronic low back pain represents those pathologies in which backpain is present but there is no evidence of a serious underlying condition as described in categories i-iii. Adequate discrimination between these groups is clinically relevant as it dictates treatment [77].

2.2.2. Epidemiology and the socioeconomic burden

The prevalence of low back pain in the Western World varies between 10% and 30%, and a lifetime prevalence of 65–80% has been reported in adults living in the United States [78,79]. In 2010, 26% of all adults participating in the mandatory nationwide health insurance system in Germany sought medical help at least once because of low back pain [80]. Chronic pain is therefore considered as an important medical condition worldwide, leading to substantial disability and related enormous socioeconomic burden[5]. Chronic pain is responsible for the highest number of years lived with disability of all chronic medical conditions [1,2]. Furthermore, chronic pain has massive direct and indirect financial consequences as it is also the most expensive cause of work-related disability [3,4].

Among chronic pain patients, chronic low back pain is a key contributor to their overall morbidity and disability. In the primary care situations, the vast majority of patients (about 90%) are diagnosed with the nonspecific low back pain type [81,82]. Low back pain is a substantial burden for individual patients and society. According to the 2016 Global Burden of Disease Study, low back pain was the leading cause of years lived with disability (YLDs) and ranked among the top ten causes of YLDs in all 188 assessed countries[2]. Balague et al. reported that 80% of adults in the Western world suffer from low back pain at some point in their lives[83].In a systematic review of 165 studies from 54 different countries, the mean point prevalence of low back pain in the general population was approximately 18% and the one-month prevalence of low back pain was approximately 30%. The lifetime prevalence of back pain approaches 40%. High prevalence was encountered in patients aged between 40 and 80 years. In addition, low back pain occurs more frequently in females than in males [84].

Not all patients with an episode of acute back pain will suffer from chronic complaints and classify for CLBP. Although, approximately 20% of people affected by acute low back pain do develop a chronic low back pain with persistent symptoms even after one year [85].

Several risk factors for developing CLBP have been identified previously. Socio-economically disadvantaged groups are much more likely to report persistent pain and substantial interference with daily functioning than socio-economically advantaged counterparts [12,86]. Alternative risk factors for CLBP are work related factors, psychosocial distress, depressive mood, severity of pain and functional impact, prior episodes of low back pain, extreme symptom reporting and patient expectations, are predictors of chronicity [87,88.]

As previously highlighted, the social and economic costs of back pain are high, and indirect costs are usually higher than direct medical costs. The indirect costs due to productivity loss represent a large proportion of the overall cost; a systematic review of 27 disease-related costs revealed that back pain has a major impact on indirect costs, which can represent 50–89% of the total costs [89].

The economic burden of low back pain is estimated to be around £2.8 billion in the United Kingdom [90] and exceeding AU$4-8 billion in Australia [91]eachyear. In the United States, the annual expenditures for the medical treatment of individuals suffering from low back pain are estimated to exceed US$ 100 billion [92]. A retrospective analysis of nearly 2.5 million patients in the United States with newly diagnosed low back or lower extremity pain between 2008 and 2015 [93], revealed that 98.8% of cohorts were treated conservatively and did not undergo surgery in the year following diagnosis. The non-surgical cohort accounted for 26.3% of the total annual costs (US$498 million) compared with US$265 million annually for the surgical cohort [93]. Approximately two-thirds of the economic costs of low back pain are indirect costs such as loss of productivity [94]. Mutubuki and colleagues [95] found that female sex, young age, multiple causes, poor quality of life and high disability were predictive of high societal costs among patients with chronic low back pain [95]. Another study showed that expenditures from presenteeism (i.e. attendance at work with suboptimal performance) were higher than direct medical costs [96]. The nature of low back pain could also result in additional, less quantifiable costs, such as difficulties with domestic chores, caregiving, engaging in recreational activities, relationships, depression, and anxiety [97].

2.2.3. Anatomical features of the lumbar spine (low back)

I. Functional structures and properties

The lumbar spine has key functions. The first and most important function is to provide mechanical support for the upper body. Form follows function, and therefore the five lumbar vertebrae are relatively oversized compared toother segments of the spine. This allows for better absorption of axial forces from the upper body. Furthermore, the spine has three different pillars, and these pillars support efficient force distribution in various positions. In addition, the spine forms a protective shield for neural structures (the spinal cord and nerves). The lumbar spine also facilitates diverse types of truncal motion without endangering the neural structures nearby the osseous spine: flexion, extension, rotation, and side bending. From a lateral view, the lumbar spine has a concave curvature called lumbar lordosis. This curvature is variable in degree and transfers the upper body mass over the pelvis to allow for efficient bipedal motion [98-100]. The lumbar vertebrae have multiple anatomical and functional components. Anteriorly lies the vertebral body, whereas dorsally to the vertebral body are located two pedicles attached to the laminae. Pedicles transmit forces from the posterior elements to the vertebral body and, together with the laminae, protect the spinal canal. At the junction of two laminae, spinous processes extend to the posterior, and at the junction between pedicles and laminae, four articular processes and four transverse processes are found [99].

The unilateral combination of superior (of the caudal vertebra) and inferior (of the cephalad vertebra) articular processes forms the facet joints (zygapopheaseal joints). These small joints between different levels of vertebrae are essential for flexion and extension [101]. In between the endplates of two vertebral bodies, lumbar discs are located. These discs are fibrocartilaginous structures that are composed of an internal gelatinous nucleus pulposus and an external fibrous annulus fibrosus. Vertebral discs are important for force distribution and shock absorption. Anterior and posterior to the vertebral body, two longitudinal ligaments are located. The ligaments provide additional support and contribute to optimal force distribution during mechanical stress. The anterior longitudinal ligament resists lumbar extension, translation, and rotation, whereas the posterior longitudinal ligament resists lumbar flexion. Additional segmental ligaments are the ligamentum flavum and the supraspinous and interspinous ligaments[101,102]. The anatomy of the lumbar spine is shown in Figures 1-3.

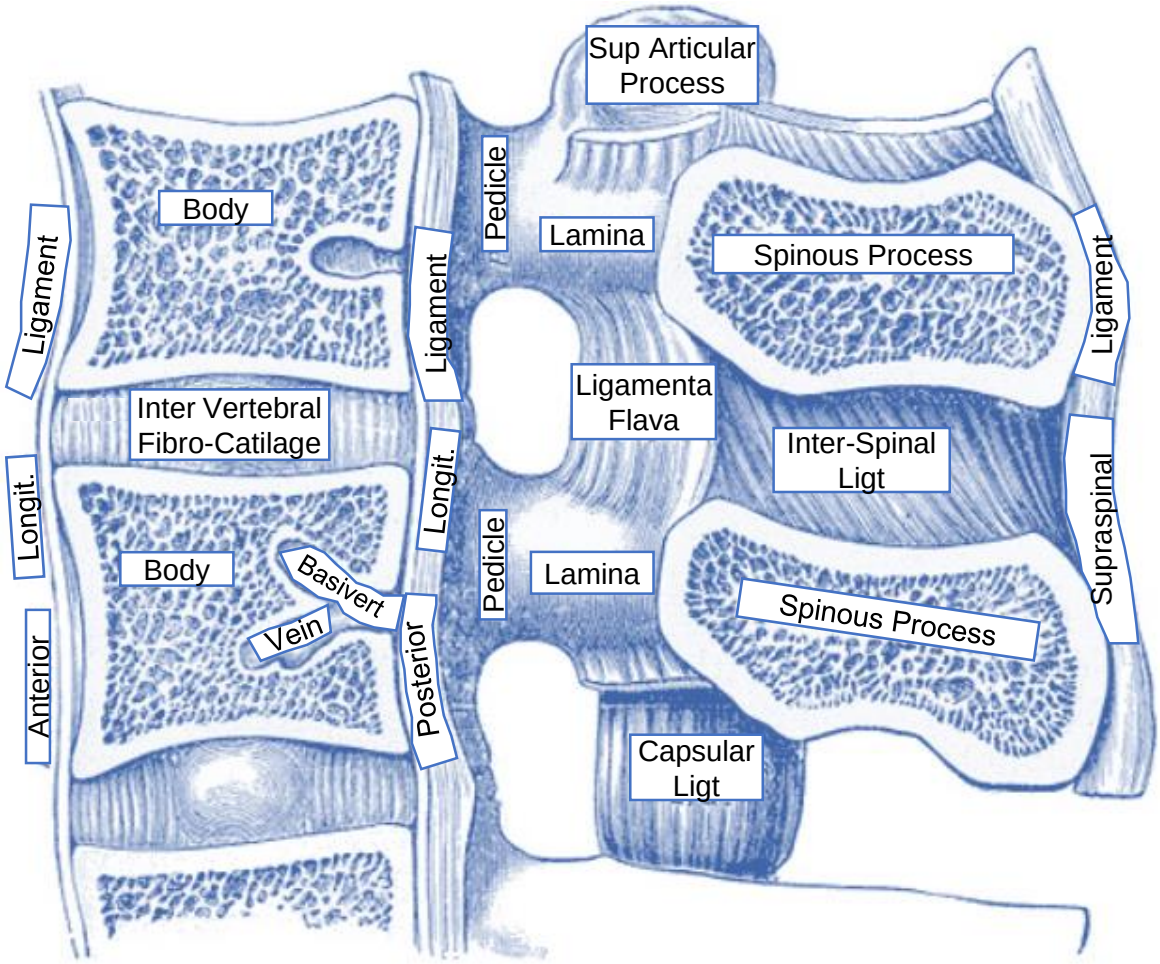

Figure 1: Medial Sagittal Section of the Lumbar Spine. Modified version of images contributed by Gray's Anatomy Plates[103].

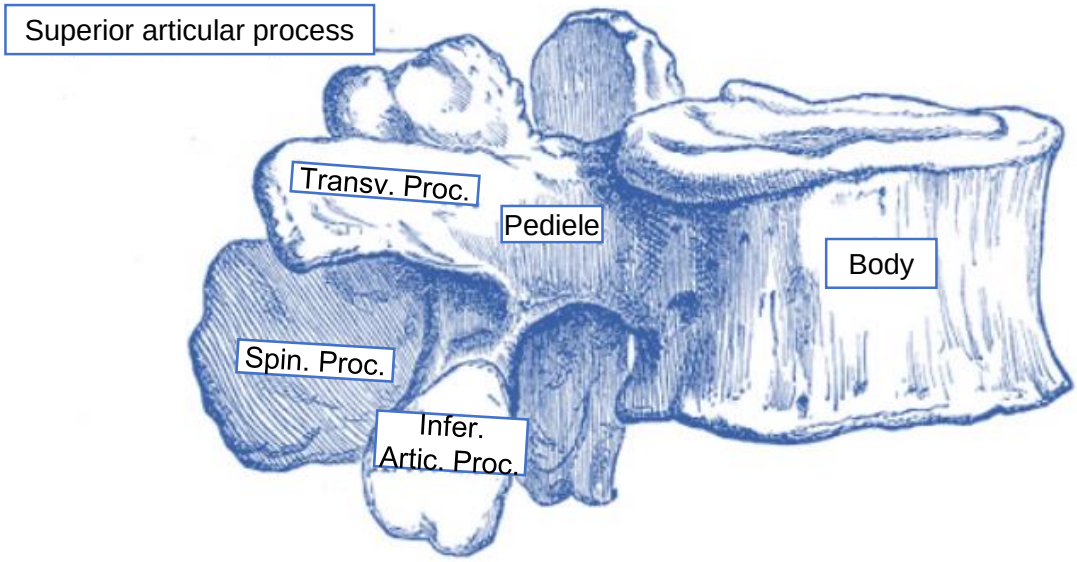

Figure 2: A lumbar vertebra from the side. Modified version of images contributed by Gray's Anatomy Plates [103].

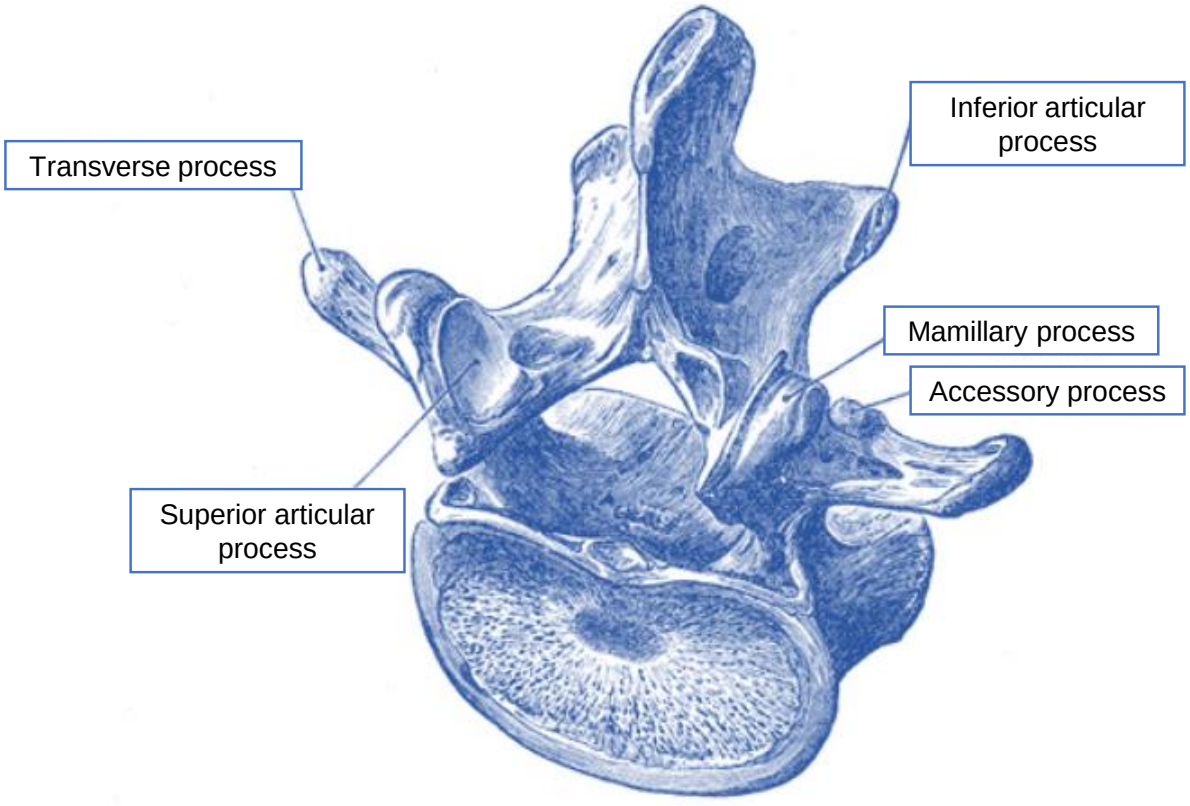

Figure 3: A lumbar vertebra from above and behind. Modified version of images contributed by Gray's Anatomy Plates [103].

II. Blood supply and lymphatics

The spine and spinal cord are highly vascularized structures with three main arteries providing vascularization. One anterior spinal artery supplies the anterior two-thirds of the spinal cord, and two posterior spinal arteries supply the posterior third of the spinal cord. Furthermore, interconnection occurs as radicular arteries run both anteriorly and posteriorly, providing collateral flow. Nerve roots are also supplied by radicular arteries that run adjacent to the nerve roots. One specific artery, known as the Adamkiewicz artery, is the largest radiculomedullary artery and has a heterogeneous anatomy, with many physiological tract variations described. In general, the Adamkiewicz artery starts at the T8-L2 level as a branch from either a posterior intercostal or a radicular artery and runs on the left side of the spinal cord before it joins the anterior spinal artery [104].At the level of the number of lumbar arteries varies between three and five pairs[105,106]. Most frequently, eight lumbar arteries arise from the posterolateral aspect of the abdominal aorta, opposite the four lumbar vertebrae and they run in pairs on the posterior side of the vertebral body. Occasionally , a fifth smaller pair may arise from the median sacral artery [107]. Branches from these arteries also perfuse the local soft-tissue compartments (fat, subcutaneous and musculature). Lymph drainage is present along the inferior vena cava and the aorta, receiving drainage from the common iliac nodes [104,106].

III. Nerves

Nerve pairs with both motor and sensory fibers exit the spinal cord at each individual level on both sides of the vertebral body. The nerve branches then pass through the neural foramen into the ventral and dorsal rami. The ventral rami are made of motor-sensory fibers for the prevertebral musculature and the lower extremity, whereas the dorsal rami allow for motor innervation to the erector spinae musculature and sensibility of the skin of the back[108]. The thoracic 12 to lumbar 4 ventral rami form a nerval interplay which is called the lumbar plexus, which gives rise to the obturator (L2–L4) and femoral (L2–L4) nerves, respectively. The remaining nerves of the lumbar plexus include the iliohypogastric (T12–L1), ilioinguinal (L1), genitofemoral (L1–L2), and lateral femoral cutaneous nerve of the thigh (L2–L3). The lumbosacral plexus forms from the L4 to S4 ventral rami. The L4 and L5 roots join to form the lumbosacral trunk, which descends into the pelvis to join the sacral plexus. The lumbosacral plexus then gives rise to the sciatic nerve (L4–S3), which branches into the common peroneal and tibial nerves. The sacral plexus also includes the superior gluteal (L4–S1), inferior gluteal (L5–S2), posterior femoral cutaneous of the thigh (S1–S3), and pudendal nerve (S1–S4) [109].

Each lumbar spinal nerve exits below its corresponding vertebra, for example, the L4 nerve exits below the L4 vertebra through the L4neural foramen.

IV. Muscles

The lumbar vertebrae serve as attachments for a large number of muscles. The muscles provide axial stabilization, protection, proprioception, and enable controlled spinal movement in different functional planes. Three main muscle groups are of utmost importance for these muscular functions. First, the extensor muscles (erector spinae and the multifidi) are located posteriorly to the lumbar spine. Contraction of these muscles (including the longissimus thoracis and iliocostalis lumborum) lead to spinal extension. Secondly, the flexor muscle group is located anterior to the spine and is important for trunk and hip flexion. The psoas major muscle originates from the transverse processes of T12–L4 and joins with iliacus to form the iliopsoas muscle. This is the major muscle responsible for hip flexion. Abdominal muscles—internal/external oblique and the rectus abdominis—are responsible for flexion of the spine. Rotation and lateral flexion of the spine are caused by the quadratus lumborum, psoas major in combination with the previously mentioned abdominal muscles [110].

2.2.4. Pathophysiology

Lumbago or low back pain (LBP), is a common symptom that affects the bones, nerves, and muscles of the back between the bottom of the ribs and the lower gluteal fold [83].

There is no clear physical cause for most lumbar plexus (low back) pain, but it is supposed to be due to non-serious muscular or skeletal problems such as sprains or strains [111]. A main cause of lumbago is considered to be muscle stiffness after jerky or awkward movements or after incorrect or excessive strain. It is favored by underdeveloped back muscles and the accompanying functional instabilities and overloads. Other physical causes of low back pain include osteoarthritis, degeneration of the intervertebral discs or a herniated disc, fractured vertebrae (e.g., due to a physical incident and/or osteoporosis) or, infrequently, an infection or tumor of spine-related tissue. The symptoms of lumbago pain can therefore originate from many different anatomical sources, including muscles, nerve roots, bones, fascial structures, joints, intervertebral discs and tissue within the abdominal cavity. The multifidus muscles run upward and downward along the spine’s backbone and are necessary for keeping the spine straight and stable during general movements like sitting, walking, and lifting. A common problem with these muscles occurs in people with chronic low back pain, when the back pain causes the person to use the back muscles incorrectly to avoid the initial pain. Often the issue with the multifidus muscles persists after the pain has subsided and is likely to be a major reason for the pain recurring [112].Discogenic back pain describes back pain associated with the intervertebral disc degeneration without herniation [113],which occurs when vessels and nerve fibers grow into the disc tissue, particularly into the fibrous ring of the intervertebral disc. Pressure-dependent back pain is the result [114]. In an advanced stage, osteochondrosis

may develop, describing the wear of the intervertebral disc with a response of the adjacent vertebral bodies.

Chronic low back pain (CLBP) is a complex condition with great heterogeneity and is frequently not caused by a single specific source. Instead, it should be considered as a broad complaint resulting from a variety of different underlying problems of varying severity [9]. Therefore, among the various structures potentially involved in chronic low back pain, answering the question "What is the pain trigger?" is a key point in treating patients suffering from it. However, this diagnostic process can be challenging as multiple sources may contribute to back pain. Additionally, pain types may change over time due to compensatory mechanisms (altered gait and pelvic balance) leading to novel pain types. Peripheral tissues such as facet joints, intervertebral discs, tendons, muscles, ligaments, synovium, joint capsules, and fascia, can all serve as initial causes of low back pain. Inflammation, injuries or degeneration of the aforementioned tissues can trigger signaling cascades that directly stimulate the nociceptors, causing acute pain. Direct damage of the spinal nerve root and pathological incursion of that nerve due to a damaged lumbar intervertebral disc can also lead to neurogenic chronic low back pain. A combination of different pain types is frequently observed, and nociplastic pain type can occur either in isolated or in combination with the previously mentioned pain types in CLBP [74,115].

2.2.5. Types of low back pain based on specific pain stimuli

Despite the work done by the International Association for the Study of Pain [116], there is ongoing debate in the field regarding the definitions of back pain, referred pain, radicular pain, and radiculopathy. The definitions and criteria utilized in the literature vary.

Identifying the primary cause of CLBP requires an accurate diagnostic work-up, especially given the involvement of multiple physicians with their own specialized knowledge and treatment strategies. Suboptimal diagnostics, leading to false claims and diagnoses, can result in the engagement of the wrong specialists and the initiation of therapies focused on managing the symptom (pain) rather than addressing the pain generators. This may ultimately lead to impaired long-term success and put the patient at risk of developing additional types of pain[117].The following is an overview of the different types of pain relevant to CLBP, including their specific pain generators and characteristics [73,118].

I. Discogenic pain

According to the study “Effectiveness of thermal annular procedures in treating discogenic low back pain” of Manchikanti et al., disc degeneration (DD) is the source of CLBP in 39% of patients [119]. Discogenic pain manifests as non-specific, axial pain symptoms without radicular radiation and non-spinal malalignment or instability. Similar to other sources of mechanical pain, discogenic pain can extend into the upper and occasionally lower legs in a non-

dermatomal pattern. Frequently discogenic pain is diagnosed only after all other pain types have been excluded. The pathophysiology has not been described in detail yet, but disc degeneration due to a degradation of disc components appears to play an important role [120].

Intervertebral discs, which are up to 80% aqueous under healthy physiological conditions, have multiple layers: an outer annulus fibrosus and an inner nucleus pulposus. The intervertebral disc is innervated by the dorsal root ganglion (DRG) and by sympathetic and parasympathic ganglia [121]. In a normal intervertebral disc, only the outer third of the disc fiber ring is innervated. However, due to the high concentration of local neurotrophic factors (e.g. nervous growth factors) and vascularized granulation, the degenerated intervertebral disc may cause the pathological spinal nerve fibers to infiltrate deeper into the inner intervertebral disc, also known as “deep nerve growth”, which can lead to intervertebral disc related pain [115,122].

In addition, the concentration of mechanoreceptors and neurons filled with calcitonin-stimulated peptides increases in the intervertebral disc of patients with chronic discogenic pain[123,124].As the sinus nerve invades the nucleus pulposus, degeneration-induced inflammation of the intervertebral disc further stimulates nerve release from the infiltrating terminal nerves [13].Sympathetic fibers are also distributed around the endplate, the annulus, the anterior spinal artery, and the vertebral body. Furthermore, a large number of nociceptive fibers within the intervertebral disc ring of the lower lumbar spine cross the sympathetic trunk in a non-segmental manner and are an important part of the sympathetic nervous system. These peripheral terminals show a prevailing expression of the so-called “calcitonin gene-related peptide” [125].Intervertebral disc degeneration followed by inflammation and the successive intrusion of nociceptive nerve fibers into the inner disc, or additional protruding tissue applying mechanical pressure on the nerve root, may be a main cause of chronic low back pain[126]. Previous studies have shown that nerve root injury and neuronal sensitization play a crucial role in the development of chronic pain in degenerative intervertebral disc disease [114,115,125,127]. In response to inflammatory stimuli, activated macrophage immune-cells in the intervertebral disc can absorb the surrounding tissue and trigger the release of further inflammatory mediators that stimulate and increase the production and sensitization of nociceptors in the nerve roots. Thus, increased afferent stimuli from sensitized nerve root nociceptors can increase neuronal reactivity in the central nervous system, leading to central sensitization and to the development of nociplastic pain [128].Furthermore, inflammation and especially damage-associated molecular patterns (DAMPs), including hyaluronic acid and fibronectin fragments, play a role in the development of discogenic pain. These DAMPs are key players in the initiation of local sterile inflammation as they modulate the action of both pro-inflammatory cytokines (such as IL-1beta, IL-6, and IL-8) and matrix degrading enzymes (MMP-1, MMP-3, and MMP-13) [120]. Metabolic risk factors for degenerative disc related pain

have also been described, and diabetes mellitus increases the risk of discogenic pain. It was hypothesized that advanced glycation end products (AGEs) are involved as they boost catabolism and inflammatory responses [129].

Intervertebral discs are essential for shock absorption, pressure distribution during axial loading, and dealing with torsional forces. Due to micro-injuries restorative processes are needed. Neovascularization is required to foster healing. A potential disadvantage of neovascularization is concurrent stimulation of mechanical and chemical sensitization [113]. Magnetic Resonance Imaging (MRI) is capable of detecting edema in the vertebral body or endplate alterations, including disc space narrowing. However, these changes are not specific for discogenic pain [130].

II. Lumbar spinal stenosis pain

The normal diameter of the spinal canal varies between 15 and 27 mm. Patients with a spinal canal diameter of less than 12 mm may already develop complaints, whereas the cut-off value for an absolute spinal stenosis is 10mm [131]. Cut-off values for the height of the neuroforamina are 20—23 mm, and impairment is expected in widths of less than 15 mm. Symptoms result from compression of neurovascular structures in the spinal canal and neuroforamina. The size of the spinal canal varies among individuals and tends to decrease over time[132]. Other factors that can cause narrowing of the spinal canal narrowing include inflammation or scar tissue from infection or surgery, disc degeneration, progressive malalignment of the spine, listhesis, ligamental hypertrophy, or a combination of these.

In geriatric patients, degenerative lumbar stenosis (LSS) is the most frequent reason for spinal surgery[133]. Symptoms include: midline back pain, radiculopathy with neurologic claudication, motor weakness, paresthesia, and impairment of sensory nerves [134].

Depending on the progression of the degeneration and the localization of the stenosis, different patterns of pain distribution may be observed. In the early stages, the majority of patients describe recurrent low back pain due to disc degeneration and to synovitis, the onset of facet arthrosis. In late stages, the low back pain becomes constant and can radiate to the flanks and gluteal region [135].

Complaints vary according to posture, because different positions are associated with change in the spine canal width. Prolonged standing or extension of the lumbar spine is commonly associated with increased pain. Pain relief is noted with sitting [136]. Neurological claudication is a typical symptom of LSS. This is due to venous pooling and hypertension near the nerve roots[134,136]. Diagnosis is based on medical history, clinical examination, and imaging [134]. The stoop test may be helpful in the diagnosis, as can radiologically imaging, which can contribute to the diagnosis, although the clinical presentation is dictates the diagnostic process [136,137].

III. Facet arthropathy (facetogenic) pain

Facet joints, or zygapophyseal joints, form the direct connection between two vertebrae and are essential in limiting movement in the young. In the elderly, these joints may also take over the force and shock absorption functions of other degenerated parts of the spine. Degeneration of the lumbar facet joints can lead to osteoarthritis and pain [138].,Regarding the pain distribution patterns of lumbar facet pain, higher lumbar joints cause non-dermatomal referred pain projecting into the hip, flank, and lateral aspects of the upper thigh. For patients suffering from facet joint pain in the lower levels of the lumbar spine, the pain is described as more lateral and posterior in the thigh. The L4/L5 and L5/S1 zygapophyseal joints are most frequently affected[139]. Furthermore, the lumbar facetogenic chronic back pain is clarified in more detail in section 2.3.

IV. Spondyloarthropathies

Systemic disease may also lead to spinal pain. Spondyloarthropathies are a common source of back pain. This group of rheumatic diseases includes ankylosing spondylitis and psoriatric arthritis, and systemic inflammation affects spinal pain modulation. Typically, multiple joints or levels of the spine may be involved and some specific features have been identified and described in the literature. Ankylosing spondylitis is most frequently found in the lower back[140].

V. Sacroiliac joint pain

The sacroiliac (SI) joint is the connection between the spine and the pelvis, and vertical, horizontal, and rotational stability is provided by several strong ligaments and a fibrous capsule in the anterior lower third of the joint [141,142]. Both these ligaments and the capsule have nociceptors that may get stimulated. Innervation of the SI joint is relatively unclear, and both anterior and posterior lumbopelvic rami may be involved [141-143]. SI pain is most common in the buttocks but can also radiate down the leg. This pain is typically worse when sitting [144]. Movements of the sacral joints affect the axial position of the spine and thereby influence other spinal segments. Both intra- and extraarticular sources of SI pain have been described, with the former being more frequent in the elderly and the latter more frequently seen in the young. Pain could be due to tension of ligaments or the capsule, compression, myofascial sources, or altered osseous forces [145]. Intraarticular sources of SI pain include osteoarthritis, whereas common sources of extraarticular pain are ligamentous injuries and enthesitis. Besides the anamnesis, the physical examination is essential in the diagnostic work-up. The movement and stability of the joint and the impact of inclination and local pain should be tested, and the patients should be asked if these tests reproduce the pain [118]. MRI investigations show effusion and inflammation, and in the case of bilateral presence an additional systemic rheumatic disease is to be considered [77].

VI. Myofascial pain

Myofascial pain can result from overuse or underuse of the back, muscle disease, trauma, haematomas or muscle tears. Diagnosing myofascial pain is challenging and there are no clear diagnostic tests. It has been shown that both atrophy and increased myoelectric activity are associated with abnormal low back muscles, suggesting combined under- and over-activation of the same muscle groups [146,147]. Due to the difficulties in diagnosing myofascial pain, most of these patients are diagnosed with non-specific back pain.

VII. Nociplastic pain

In addition to the specific causes of low back pain mentioned above, there is a significant subset of patients for whom a definitive diagnosis cannot be made. These patients are often referred to as the non-specific low back pain group. This refers to the absence of a specific source of pain, or a source that cannot be identified by routine diagnostics. In the past, up to 90 % of patients were diagnosed with non-specific low back pain, but these rates have decreased with the development and introduction of additional diagnostic tools such as diagnostic blocks, advanced imaging, and neurophysiological studies [77]. Furthermore, many patients with unclear pain generators have been classified as myofascial [146].More recently, however, a new group of pain has been introduced and defined: nociplastic pain. Sensitization plays an essential role, and diagnosis can be made in the absence of a clear pain generator. Nociplastic pain can occurs imultaneously with other pain types as well [148].

2.2.6. Psychosocial factors aggravating low back pain

The previously mentioned sources of back pain can be significantly affected by psychosocial factors as well. These psychological factors should be taken into consideration when defining treatment plans as they can greatly modify success rates. Chronic low back pain may be exacerbated by the activation of psychological coping mechanisms to deal with localized pain and tenderness in the lower back. Systemic coping mechanisms may affect local pain sensation and can even trigger regional and generalized hyperalgesia, allodynia, and other neuropathic phenomena [149]. As a result, central pain processing may change, and this is associated with altered central pain processing in the long-term. Potential secondary consequences include fatigue, insomnia, and other psychological and behavioral changes, which may further have a negative impact on the local low back pain symptoms [149]. Specific psychological diagnoses associated with chronic low back pain include depression, anxiety and substance abuse [33,150,151]. Psychological issues and specific pathologies are also associated with social problems, and patients with chronic low back pain have higher rates of disability, drug abuse, medicolegal problems and incapacity for work [150].

2.2.7. Therapies and treatments of CLBP

CLBP can be treated with a variety of therapies and medical interventions, which can also complement each other. For example, behavioral therapy is often used to reduce disability by addressing maladaptive pain behaviors and cognitive processes [10]. This can be combined with established physical exercises, regardless of the patient's physical condition and the chronicity of the disease, as they have proven effective in improving back locomotor function [11].

Pharmacological treatment of low back pain should start with the maximum recommended dose of non-steroidal anti-inflammatory drugs, followed by complementary medications such as muscle relaxants, tramadol, corticosteroids, and even short-term opioids for moderate to severe pain, according to the WHO stepwise plan for the management of chronic pain [12-14].

If conservative treatment fails to relieve symptoms, more invasive treatments are usually include radiofrequency denervation of the medial branches supplying the joints, intra-articular steroid or anesthetic injections, cryotherapy, and chemical neurolysis with various agents (ethyl alcohol (50–100% v/v), phenol (5–10%), or glycerol (20–100% v/v)) [152-154].

Intra-articular injection of ethyl alcohol not only inactivates chondrocytes, but is also reported to cause neurolysis and, additionally, destruction of sensory innervation of the synovium, the joint capsule, and possibly subchondral bone. The neurolytic effect of ethyl alcohol is commonly used in human medicine for patients with chronic pain syndromes [155]. This effect is caused by the extraction of phospholipids and cholesterol from the cell membrane, along with unfolding and denaturing of lipoproteins and mucoproteins. Alcohol chemical neurolysis usually results in blockade that continues for 3–6 months and has been used for peripheral nerves and plexus blocks [156,157]. The most frequent documented side effect of alcohol neurolysis is local pain at the injection site for 24–48 hours. Further reported side effects include swelling, dysesthetic pain, infection, and soreness. While intra-articular steroid injection therapy and medial branch blockade with steroids provide effective temporary pain relief, long-term results are suboptimal [16,156,158,159]. The role of chemical neurolysis in the prolonged treatment of low back pain with various concentrations of ethyl alcohol, phenol or glycerol is controversial. In 2010, the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine recommended that chemical neurolysis should not be used in the routine interventions of patients with chronic pain syndrome [34].

Since 1976 [160],radiofrequency denervation procedures have been further improved and are now a widespread application for treatment of low back pain syndromes [161-164].Radiofrequency denervation is basically a physical technique that modulates the neural transmission of nociceptive stimuli to relieve spinal pain. It intends to deactivate nerve fibers assumed to contributing to pain perception and transmission by applying a local cellular

electrical current and high local temperatures to inactivate sensory nerves through heat denaturing, thus preventing the transmission of nociceptive impulses [32] .There is moderate to strong evidence that radiofrequency denervation provides both short- and longer-term relief of low back pain originating in the facet joints [33].

2.3 Lumbar facetogenic chronic back pain

2.3.1. Historical background and epidemiology

Low back pain (LBP) can have multiple causes, and there may be an interplay between different types of pain. Research, both clinical and pre-clinical, has improved our understanding of the pathophysiology of LBP. Facet syndrome, a specific entity of low back pain (LBP), is now widely accepted as a cause of back pain. The term 'facetogenic pain' was first used in 1911 by Goldthwaite to describe this type of pain [6].Ghormhley was the first to define facetogenic pain as a source of low back pain by introducing the term “facet syndrome”[7]. Initially, the definition was limited to lumbosacral pain with or without sciatica, and as the definition evolved into the current definitions, Badgley suggested already in the first half of the 20th century that facet joint pain was responsible for up to 80% of back pain [165]. The facet syndrome can be present not only in the lumbar portion of the spine but also in all segments of the spine [31]. Inconsistencies in criteria for diagnosis result in varying prevalence rates in literature, ranging from 5% to 90% [6,7,166,167]. Using current diagnostic criteria in a well-defined patient population, Kleef et al. demonstrated a prevalence of 5–15% of the facet syndrome in patients diagnosed with axial low back pain [168]. In patient populations with CLBP, the prevalence of lumbar facetogenic pain varies from 27 to 40% [8].

In a population of patients with CLBP, a systematic review demonstrated that facet joints were considered to be the primary pain generator in 10–15% of patients, whereas in the elderly,40% of patients identified the facet joints as the main pain generator [169]. As arthritis is associated with the development of facetogenic pain, the prevalence of facet syndrome also increases with age [168].

2.3.2. Detailed lumbar facet joint anatomy and biomechanical function

I. Anatomical Features

A spinal segment consists of two vertebral bodies, an intervertebral disc, and bilateral dorsally located joints. Together, these form a triangular joint complex that allows for smooth movement and stability in different postures. It is important to maintain a balance between the anterior joint and the posterior paired joints to prevent progressive degeneration and the development of multiple joints at the same level. Degenerative changes in one joint may lead to gradual degeneration of the other joints in the same segment. It is important to note that this degeneration may occur concurrently.

A single facet joint has both a superior articular process that connects with the lower vertebral level and an inferior articular process that bridges with the higher vertebral level. The latter is oriented in the anterior-lateral direction, while the larger superior articular

process is oriented in a posterior-medial direction. As in most elements of the bony spine, a plethora of anatomical variations have been described. Considering that 4–30% of patients exhibit such variations in spinal anatomy, it is essential to identify them and assess their potential impact on spinal balance and the risk of increased and aberrant degeneration [170].Facet joints anatomy relates to function and therefore the orientation of the lumbar facet joints differs from more coronal areas in order to allow for greater range of motion [171]. Facet joints are relatively small diathrodial joints responsible primarily for the posterolateral articulation of the spine, connecting the posterior lamina with two vertebrae at different levels. These facet joints are the only synovial joints of the spine and also have a joint capsule. Hyaline cartilage covers the bony aspects of the joint and the synovial membrane allows for intra-articular homeostasis of the 1–2 ml synovial fluid [8,172].

II. Biomechanics

The paired facet joints interact with the anterior intervertebral disc and to facilitate stability during loading in various positions. As increased loading of the dorsal aspects of the spine occurs during extension, the anatomy should compensate for this. Therefore, bone thickness and surface are not homogeneous. Degeneration may further boost load transmission along the dorsal axis. In healthy spinal segments, 3–25% of segmental load is being transferred via the facet joints and the remaining load is transmitted via the anterior compartment of the spine. This percentage of dorsal loading, however, can double (up to 47%) in the case of degeneration [31,173]. The dorsal facet joints also counterbalance motion under loading conditions which predominantly require anterior load transmission. Thus, the facet joints should also be considered as a motion control unit or motion limiter [174]. Collagenous tissue and a thick fibrous capsule provide the additional support required to deal with forces in extended positions [172]. The combination of large forces, large range of motion in multiple directions, including rotation makes the facet joints susceptible to degenerative changes [30,175].

III. Sensory Nerve Supply of Lumbar Facet Joints

The dorsal branch of the spinal nerves has three different branches (medial, intermediate and a lateral branch)[176,177]. Regarding the segments L1–L4, the medial branch of the dorsal rami is responsible for the innervation of the lumbar facet joints. The branch passes through the intertransversal ligament and then crosses the transverse processes superiorly before entering the caudal root of the superior articulate process one level below the initial level. Thereafter, the nerve continues its course in a caudal direction and is entrapped in the mamillo-accessory ligament (MAL). Then the branch enters the m. multifidus [176,178].

The other branches (intermediate and lateral branches of the dorsal rami) run downward and in a lateral direction, entering the m. longissiumusand iliocostalis. This leads to a dual innervation pattern for all facet joints, as the medial branch both innervates the facet joint at

the same level and at an additional cranial level [179].A different innervation has been described for the L5level, as it has a longer dorsal ramus with an altered course that runs along portions of the sacrum and there is no lateral branch involved [176,177].

Experimental research has demonstrated that the anatomy and nerve supply of the facet joints is relatively heterogeneous and may be even more complex than assumed. It has been suggested that there are also additional myelinated nerve fibers located on the synovial folds which have the potency to function as nociceptors [180]. Kaplan. et al. showed in an experimental study that despite medial branch blockage, about 11% of patients still experienced suggesting more collateral innervation of the involved facet joints. This concept has also been suggested by a study from Sakuma, which demonstrated in a rat model that the L5–S1 segment has aberrant and multisegmented innervation [181,182]. Additional experimental studies further suggest a more interrelated neural supply network than the segmental distribution described before. However, besides small-sized experimental mapping studies, there is a lack of evidence on this anatomical-functional topic [105,183].The course of the medial branch of the dorsal ramus of the lumbar spinal nerve and the innervation of the facet joints (L3/4, L4/5 levels) displayed in Figures 4–6.

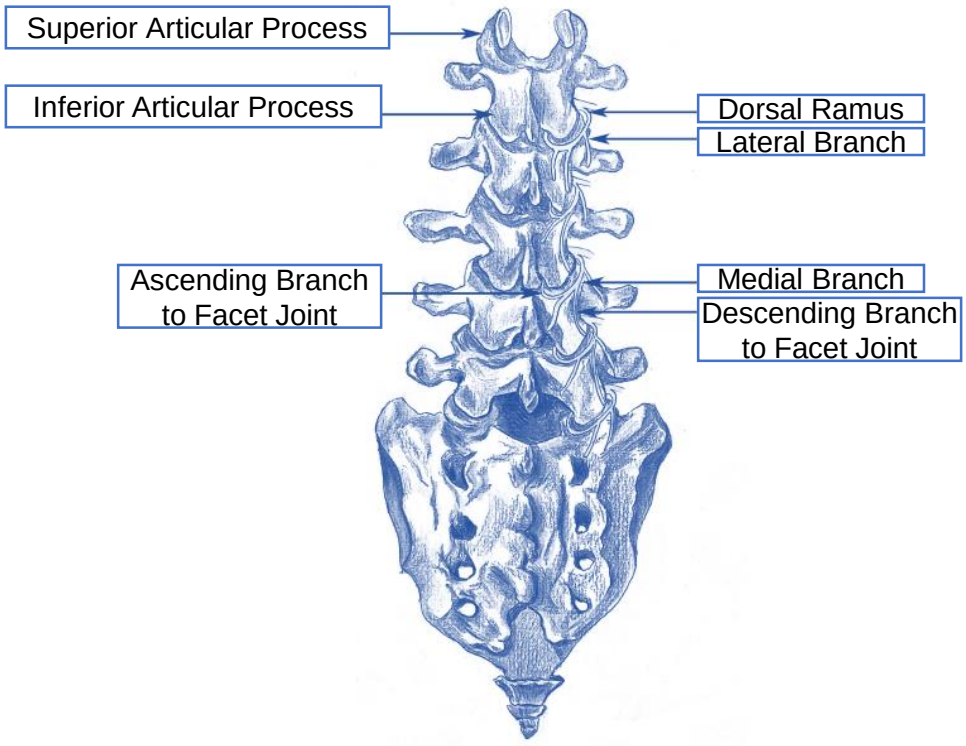

Figure 4: The course of the medial branch of dorsal ramus from the lumbar spinal nerve(modified version) [184].

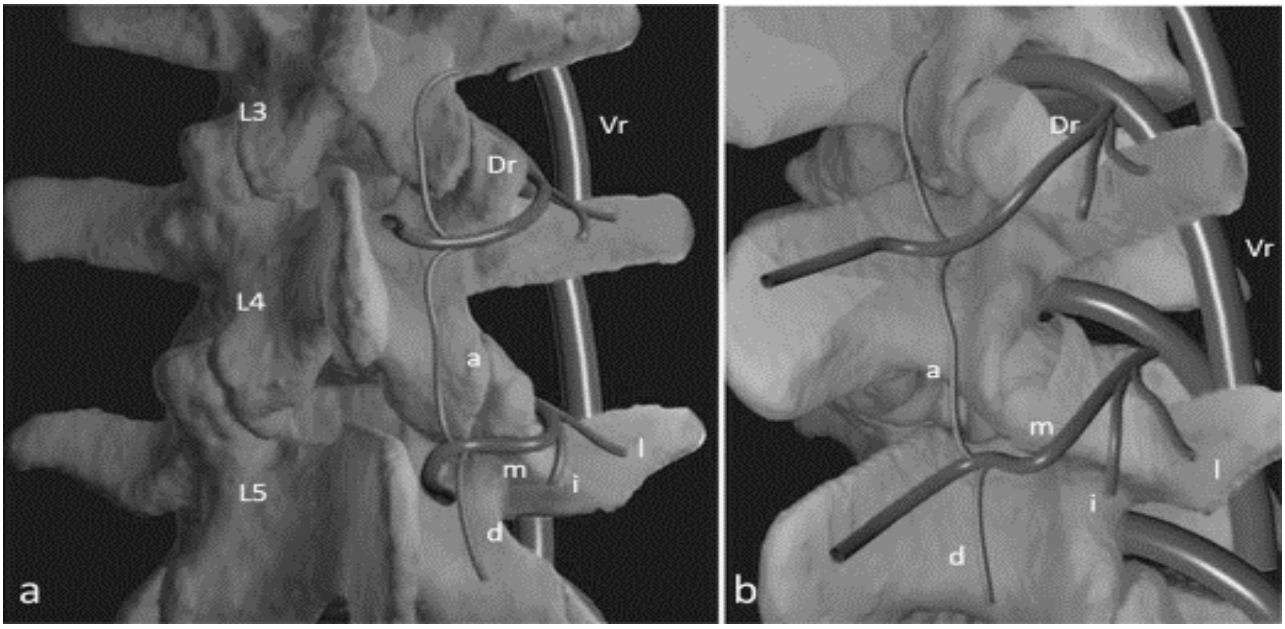

Figure 5: Innervation of facet joints of Levels L3/4 and L4/5(a) Posterior and (b) posterolateral view of the lumbar spine(modified version) [138].

Vr: ventral ramus. **Dr**: Dorsal ramus. **m**: medial branch. **i**: intermediate branch. **l**: lateral branch **a**: ascending branch. **d**: descending branch.

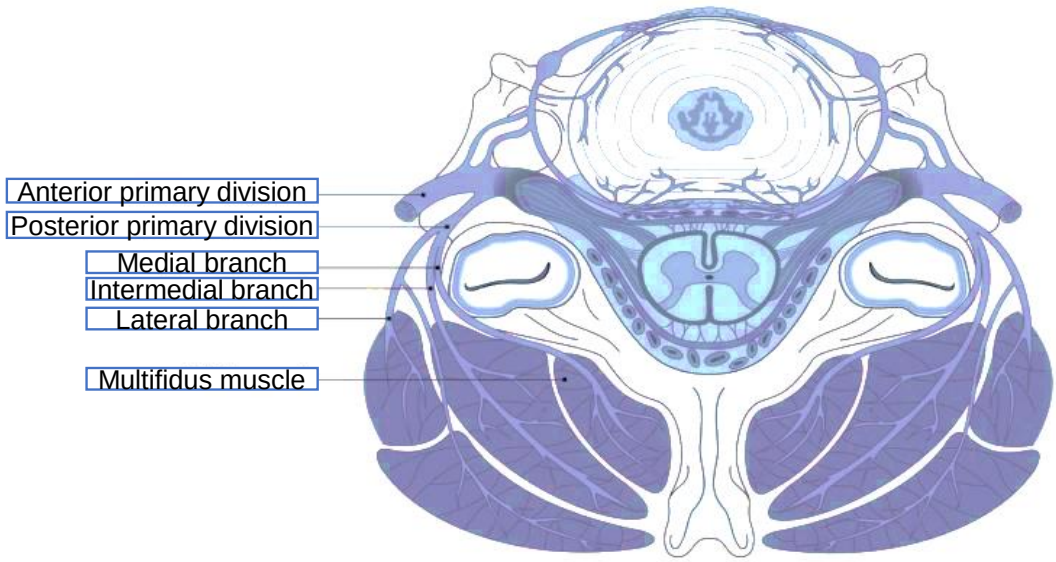

Figure 6: Diagrammatic illustration of medial branches and its course (modified version) [169].

2.3.3. Pathophysiological background of lumbar facetogenic pain

Facetogenic pain is a significant cause of low back pain, although diagnosis can be challenging due to the absence of radiographic findings. However, effective diagnostic blocks can confirm the existence of isolated facetogenic pain. Experimental studies suggest that in most patients, the pain originates from the facet joint capsule, which is highly innervated by both high-threshold nociceptive and autonomic nerve fibers [30].Excessive stimulation of nociceptors and mechanoreceptors due to high forces is considered to trigger the initial facetogenic pain sensation [31].

The chronification of back pain is associated with additional (low-grade) inflammation of the facet joints and their capsules. Pro-inflammatory signaling is enhanced due to changes in Substance-P, prostaglandins, and cytokines such as TNF-alpha, IL-1, and 6. These changes have been identified in symptomatic facet joint degeneration [185,186].Following facet joint injuries, Sakuma et al. demonstrated altered TNF-receptor expression, suggesting that inflammatory cell signaling may be affected at the receptor level[182]. However, the exact role of these findings is unclear, as the data have not been reproduced by other groups yet. High forces transmitted over the capsule may either result in direct damage to axons and subsequent pain generation[31]or lead to the transition from intermittent to ongoing stimulation of capsule nociceptors/mechanoreceptors [30],or a combination of both processes. Neurophysiological investigations on rabbit lumbar facet joint capsules and adjacent tissues led to the identification of about thirty mechanosensitive units at the lumbar facet joint, and an equal number at muscles and tendons attached to the facet joint. Despite comparable numbers of mechanosensitive units, differences in properties of the mechanosensitive units between the different compartments were demonstrated. The units found at facet joint were characterized by high-thresholds and low conduction velocities compared to the counterparts found in the other compartments [187]. In vivo induction of inflammation by the injection of Type-II carrageenan resulted in an increased receptor activation. Additional macroscopic analysis of injected joints revealed signs of local inflammation (e.g. edema, hypervascularization and white blood cell pooling) [187]. Similar findings were reported upon injection of substance P in facet joints of rabbits [188].Furthermore, the synovium also seems to contain nerve fibers [180] and it has also been hypothesized that acute (trauma) or chronic (degeneration) inflammatory processes generate pain by the synovial nerve fibers only [180]. Kim et al. further revealed in an experimental study using cadaveric models and post-operative cases that not only inflammatory but also angiogenic mechanisms are essential in the development of facetogenic low back pain [189]. Besides the previously mentioned pathological processes, aging itself also leads to structural and biological alterations and therefore the `physiological` process of ageing and related joint degeneration should also be addressed, as it affects the progress of the previously mentioned pathological processes as

well.

Osteoarthritis (OA) of the lumbar facet joint is very frequent and is associated with increased subchondral bone resorption [190,191]. However, this does not directly result in pain, although it may reduce the joint's capacity to cope with high strain forces and make patients with OA prone to develop low back pain. The relationship between osteoarthritis and chronic low back pain has been suggested by a computed tomography (CT) investigation in adult men, as a significantly higher percentage of patients with CLBP had facet joint osteoarthritis than the control group [192]. However, CT-proven facet joint osteoarthritis is not directly associated with pain symptoms and is, in fact, already present in most young adults without any back pain [191]. The highest prevalence of facet joint osteoarthritis is found at the L4/L5 level and the prevalence clearly increases with age [173,193]. More recent imaging studies revealed that there is a clear correlation between disc and facet joint degeneration; however, vice versa, isolated lumbar facet degeneration was also identified as a predictive factor for intervertebral disc degeneration later on [193,194]. Most likely, there is also a biological relevance to this finding, as a causal relationship between facet joint degeneration and future disc degeneration may rely on altered and non-physiological loading of the intervertebral disc region upon degenerative changes of the facet joints [195].

The impact of force distribution alterations on pain symptoms has also been studied in detail. Smooth movement of the spine requires a balanced orchestration of movements (flexion/extension, lateral flexion and rotation) in three planes. Different biomechanical parameters of the facet joints have been studied in an experimental setting. These parameters include the facet joint orientation (FCO) and the facet joint tropism (FCT). Changes in these parameters seem to affect intervertebral disc degeneration at lower lumbar spine levels due to early biochemical changes of lumbar intervertebral discs [196,197].More profound alterations of these parameters are further associated with increased development of osteoarthritis [196-198].

Thus, the combination of the previously described mechanical and biological processes that trigger pain sensation and the subsequent transition from intermittent to continuous pain generation appears to form the pathogenic basis for facetogenic pain. However, additional clinical and preclinical research is urgently needed to further identify the specific roles of the different mechanisms.

2.3.4. Diagnostics

I. Clincal history

The clinical course and pain history are of great importance in the diagnosis of facetogenic pain. Studies to identify specific symptoms of facetogenic pain are mainly based on the experimental induction of pain in healthy volunteers. Although these studies mainly failed to identify criteria able to discriminate pain characteristics between patients with facetogenic back pain and patients with other types of back pain [199-201]. Among patients with facetogenic pain, the most frequent symptom is axial low back pain, whereas lateral pain is associated with sacroiliac pain generators. Of note, acentric bilateral complaints have been described in patients with facetogenic pain, as well as pain in the groin area [139,199,202]. Pain extension, not radiation into other areas, has been described as well in patients with facetogenic pain. Facet joint pain from the lower lumbar spine tends to radiate into the posterior thigh. The flank and hip region may be involved in facetogenic pain originating from the higher lumbar portions of the spine [138](Figures7 and 8).

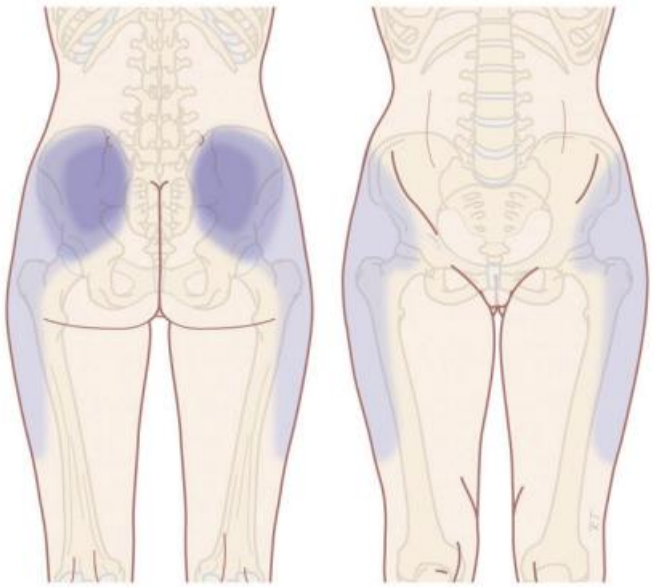

Figure 7: Pain referral pattern of lumbar facet pain adapted from McCall et al.[199].

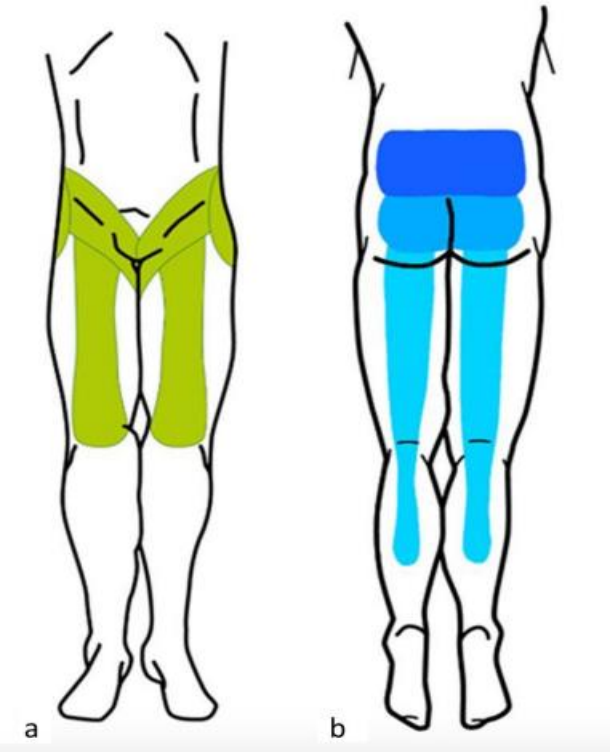

Figure 8: Facet joint pain radiation: **(a)** Green: anterior aspect of lower limb possible radiation areas, an anterior aspect of the lower limb;**(b)** Blue: posterior aspect of the lower limb, from most frequent (dark blue), to less frequent (light blue) radiating pain areas. Dark blue: pain limited to lower back. Intermediate blue: radiating pain to the posterior aspect of the buttocks. Light blue: radiating pain to the posterior aspect of the lower limbs, may extend lower than the knee level [138].

II. Physical Examination

As with the clinical course and symptoms, there are also no specific findings on the clinical examination of patients with facetogenic pain. Lumbar paravertebral tenderness has been specifically associated with facetogenic pain [203]. In addition to passive investigations, palpating and stressing the spine, active examination of the spine is important as well. The facet joints are key elements in flexion and extension of the spine and therefore pain should be tested and compared under both conditions [204]. In a study performed by Revel et al. it has been demonstrated that certain conditions are specific for facetogenic pain. These criteria are known as the Revel criteria [205]. The Revel criteria for lumbar facet joint pain are as follows:

• Pain does not worsen upon coughing, flexion, extension, rotation or hyperextension

• Pain relief in the supine position.

However, previous and subsequent studies have failed to confirm these findings [202,206]. Although it is widely accepted that lumbar paravertebral tenderness is indicative of facetogenic pain, a claim that is supported by clinical trials [203].

In 2007, an expert panel performed a review on specific diagnostic criteria of facet pain and a panel of 12 indicators has been proposed [207].These indicators include:

1. Positive response to intra-articular facet joint injection
2. Localized unilateral back pain
3. Pain relief by fluoroscopically guided double-anesthetic blocks of the medial branch of the dorsal ramus supplying the lumbar facet joint
4. Replication or aggravation of pain by unilateral pressure over the lumbar facet joint or transverse process
5. Lack of radicular features
6. Pain eased in flexion
7. Pain, if referred to the leg, is above the knee
8. Palpation: local unilateral passive movement shows reduced range of motion or increased stiffness on the side of the lumbar facet joint pain
9. Unilateral muscle spasm over the affected lumbar facet joint
10. Pain in extension
11. Pain in extension, lateral flexion, or rotation to the ipsilateral side
12. Radiology is unreliable and cannot diagnose the lumbar facet joint pain

III. Imaging findings

a) X-ray imaging: Radiographs and computed tomography (CT)

As with most orthopedic medical issues, the first imaging step includes conventional radiological x-ray investigations. For facetogenic pain, this includes three different views of the lumbar spine: AP, lateral, and oblique views [208] . The oblique imaging is superior for projecting adequate structures of the facet joints, while lateral views provide better views of the isthmus profile, such as the pars interarticularis defect. X-ray imaging may display degeneration by showing joint space narrowing, sclerosis, and calcification of the joint capsule. CT-imaging may further demonstrate additional information suggesting degeneration and is therefore superior to conventional x-ray imaging. These studies allow for high-contrast cross-sectional imaging and should be considered as standard diagnostics for spinal pathologies. CT-specific signs for degeneration include subchondral erosion, cartilage thinning, hypertrophy of the processus articularis and the ligamentum flavum. Secondary signs for degeneration include the vacuum joint sign and effusion on CT imaging [206].The presence of signs predictive for spondylolisthesis are not very specific as Kalichman et al. showed already in 24% of X-rays signs of facet joint arthritis in people younger than 40 years of age. However, no correlation with pain was found [209].

b) Magnetic Resonance Imaging (MRI)

The exact role in the diagnosis of facet joint pain or degeneration is a topic of debate, as findings from the literature differ, and no clinical studies have shown any additional benefit of MRI investigations over CT scanning in the diagnosis of facetogenic pain. Nevertheless, as MRI-studies do not expose patients to radiation, this imaging technique is considered as the gold standard for spinal imaging in general and may be a feasible alternative for the diagnosis of facet related pain in specific patient groups, such as young patients [210]. MRI studies may pick up degenerative osteoarthritis of the facet joints if there is bone edema or synovial inflammation [211]. Fluid in the facet joints or cysts are more suggestive for segmental instability than for facet joint related pain [212-215]. For the analysis of secondary degenerative issues related to facet joint degeneration, MRI-studies, have been shown to be superior to CT scanning for assessing the status of neural structures [216].MRI may also show subchondral bone edema at the facet joints of symptomatic back pain patients (in up to 40% of cases) [217,218]. Gadolinium enhancement allows the diagnosis of facet joint synovitis, although this has not been associated with pain complaints [138,211].

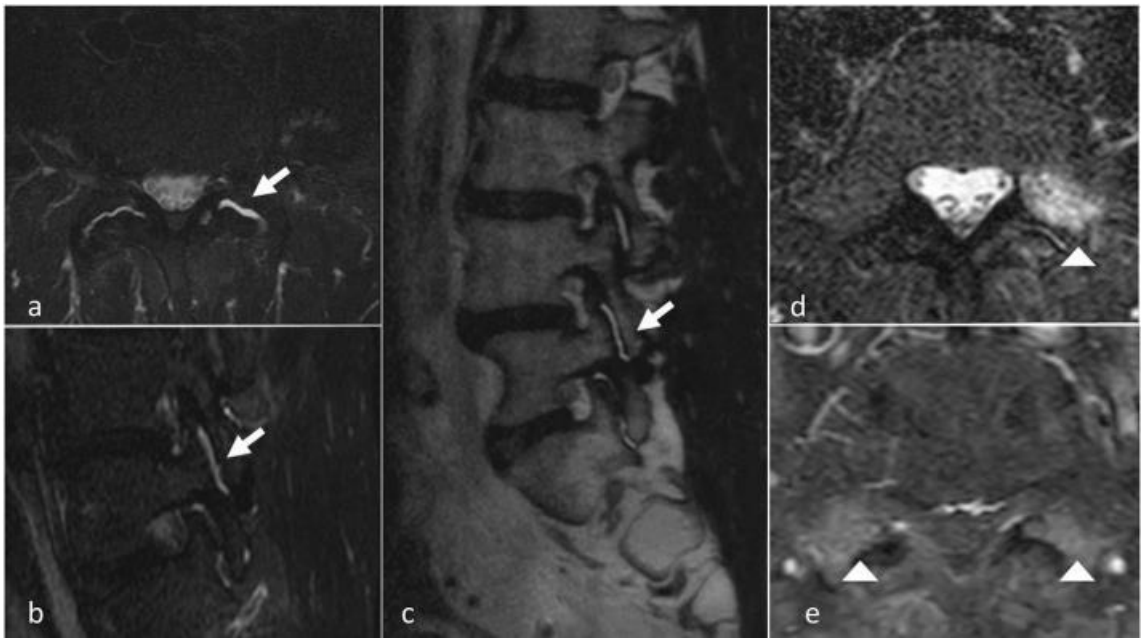

Figure 9: MRI imaging of facet joints. Active synovial inflammation and intra articular edema: axial and sagittal T2 STIR views (a, b) and T2 sagittal view (c). T2 STIR and T1 gadolinium-enhanced axial views (d, e): articular process bone edema [138].

c) Single-photon emission computed tomography (SPECT)

Radionuclide bone scintigraphy with single photon emission computed tomography (SPECT) enables the detection of increased osteoblastic activity and is considered as a functional investigation. Although osteoblastic activity can reflect microcalcifications, it also increases in response to infection, fracture healing and chronic instability. It not possible to discriminate between acute and chronic degenerative causes, except through follow-up imaging

protocols[219,220]. The feasibility of SPECT imaging for the diagnosis of facetogenic pain has been demonstrated by others [221].A sensitivity of 85-100% and a specificity over 79% for detecting facet joint arthropathy in patients with chronic low back pain has been described [221,222].A retrospective study on patients with chronic spinal pain and suspected facetogenic pain performed by Matar et al. demonstrated that hybrid SPECT with integrated CT imaging and computed reconstruction of the SPECT and 3-dimensional CT images resulted in a sensitivity of 92%for identifying the exact location of pain and the key pain generator [223].

d) Imaging classification of facet joint osteoarthritis

There are two different radiological classification systems for facet joint: the Pathria´s and Weishaupt´s classifications.

According to the Pathria-system [224] different grades can be discriminated:

Grade 1:facets with joint space narrowing

Grade 2:facets with narrowing and sclerosis or hypertrophy

Grade 3:facets with severe degenerative disease encompassing narrowing, sclerosis, and osteophytes.

Weishaupt's grading scheme [213] requires MRI or CT imaging and discriminates between grades as follows:

Grade 0:normal facet joint space (2±4 mm width)

Grade 1:narrowing of the facet joint space (< 2 mm) and/or small osteophytes and/or mild hypertrophy of the articular process

Grade 2:narrowing of the facet joint space and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions

Grade 3: narrowing of the facet joint space and/or large osteophytes and/or severe hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts

IV. Diagnostic blocks

In addition to non-invasive diagnostic tools, diagnostic injections may also contribute to the diagnostic process in low back pain. The usage of diagnostic blocks for the diagnosis of spinal pathology can be done with conventional x-ray imaging or under sonography guidance [225,226]. Regarding the localization of applied blocks for facet joints, two options and techniques have been described: intra-articular injection and medial branch blockage. Medial branch blocks are preferred in most centers as it is believed that this technique is safer and easier to perform. However, in order to confirm adequate needle placement, the benefit of intra-articular injection is that with this technique there is the possibility to inject a contrast agent as well. This can be done to confirm an intra-articular puncture [224]. No differences in specificity and sensitivity of both techniques have been demonstrated in a comparative study [227]. The overall rate of false positive findings ranges between 15 and 40%, and 11% of blocks

are believed to be false negative[19,167]. False-negative or false-positive blocks can be explained by the complex innervation patterns of the facet joints, technical failures including suboptimal needle positioning or vascular injections [181,228].Of note, most diagnostic blocks are also partly intended to be therapeutic and it has been demonstrated that medial branch blocks are associated with longer periods of pain relieve than intra-articular injections [159]. Intra-articular blocks normally require an injection of 1 to 2 ml of an anesthetic agent, as higher volumes are associated with extra-articular leakage. Medial branch blocks are easier to perform and are therefore performed more frequently [159,229]. Furthermore, medial branch blocks have better predictive value for successful subsequent neurolysis [230].Two different needle positions can be utilized: either at the upper edge of the processus transversus or in between the processus transversus and the ligamentum mammilloaccessorium. The second needle position is associated with less local spread of the anesthetic agent and therefore has a higher specificity and is used by most physicians [168,228].

Furthermore, the use of multiple diagnostic blocks is not recommended as this makes it difficult to identify the exact involved level. According to most national and international recommendations, a pain reduction of 50–80% upon diagnostic blocks is considered as a positive response. Repeated interventions at the same level may reduce the rates of false positive and false negative findings [231-233]. Literature also indicated that for the diagnosis of facetogenic-related pain, a positive response should be demonstrated at least twice after injection. It has further been reported that a single injection at a single level is associated with a false-positive rate of up to 45% [234]. The rate of success upon subsequent radiofrequency ablation of success upon subsequent radiofrequency ablation of facet joints varies from 39% after a single injection to 64% after two successful diagnostic blocks [212]. Both agents resulting in local anesthesia and a combination of these substances with steroids can be utilized for diagnostic injections [154,167].

2.3.5. Treatment of facetogenic low back pain

I. Noninvasive management:

Different treatment protocols have been developed and multidisciplinary approach is indicated for most patients. The multidisciplinary conservative treatment plan should entail four different elements:

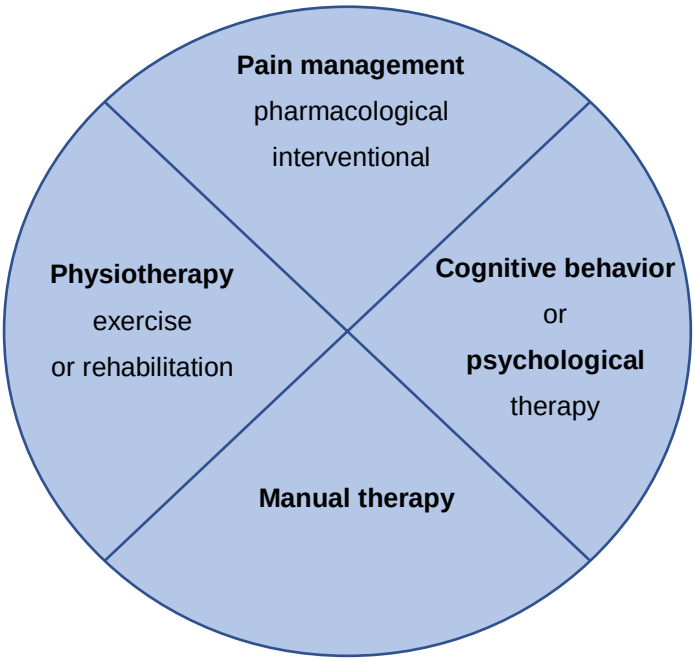

Figure 10: Noninvasive management of facetogenic low back pain.

A stepwise approach is recommended in which the different pillars of treatment are escalated over time and depending on the response to treatment alterations [168].

The first step of the conservative treatment of patients includes basic pain medication (non-steroidal anti-inflammatory drugs, muscle relaxants, and pain medication according to the WHO-scheme), as well as physiotherapy and psychological consultation [167,235]. Additional psychological consultation and antidepressants also seem to be effective in a specific subgroup of patients with chronic facetogenic back pain.

A systematic review of50 randomized controlled trials published between January 1980 and October 2002 (involving 4,863 patients) was executed to investigate the efficacy and outcome of drugs for low back pain. This study, focused on short-term outcome parameters, demonstrated only minor effectiveness of drug therapies for low back pain (including facetogenic pain). Especially, the impact of the usage of non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) on both chronic and acute low back pain was demonstrated. The usage of muscle relaxants was only beneficial for acute low back pain groups, whereas antidepressants were successful for patients with chronic low back pain only. Regarding the safety of these therapies, the findings were very heterogeneous and it was eventually

recommended that prospective trials are indicated to gain insights in both the efficiency and safety of these drug therapies. A combination of different pharmacological therapies has also not been evaluated properly [236].

II. Invasive management

As mentioned before, lumbar facet joint nerve blocks are a safe and helpful diagnostic tool to discriminate between different pain generators in patients with back pain. Additionally, local injection therapy is also utilized as a therapy for facetogenic pain as it enables patients to intensify physiotherapy and other additional therapies and thereby achieve long-lasting improvement. Besides injection therapy, other invasive techniques are also available to treat facetogenic back pain. The level of evidence for the success of therapeutic nerve blocks is currently between level II-1 and II-2 with a 1B or C/strong recommendation. Regarding alternative invasive therapeutic options (e.g. radiofrequency neurotomy), the evidence is II-2 to II-3 with a recommendation of 1B or 1C [8,27-29].

Key features of the different techniques have been summarized in this table 1 as well. A detailed description of the available treatment options follows thereafter.

Treatment modality	Characteristics
Medial Branch Blocks and intra-articular blocks	Mainly used as diagnostic tool to determine the involved level. Longer-lasting substances may contribute to anesthesia of the nerves innervating the facet joint and thereby allow for increased activity.
Steroid Injections	Steroids may be applied into the facet joints and downgrade ongoing inflammation and related pain. Pain relievers is shorter than radiofrequency ablation and a combination with intensified exercise is indicated to achieve long-lasting results. Repetitive interventions are possible, however a certain number of steroid injections per year (incl. those to other body areas) should not be exceeded.
Medial Branch Radiofrequency Denervation	Medial branch radiofrequency denervation is a minimal invasive technique in which the same landmarks are utilized as for medial branch blocks.Repetitive interventions are possible. The impact of multiple ablations decreases over time.
Capsule Radiofrequency	Percutaneous radiofrequency to the capsule of the lumbar facet joint is a relatively invasive intervention that targets the entire joint capsule. This technique may result in long-lasting pain relief.
Cryoneurolysis	Gas-cooled cryoprobes are used to freeze the involved nerves and to result in nerve dysfunction.
Chemical Neurolysis	Nerve damage is achieved by the local application of chemical substances. Regeneration of nerves may result in the development of painful neuromas.

Dorsal Root Neurotomy	Dorsal root neurotomy is a relatively invasive therapy, however does result in proper and long-lasting pain relieve compared with medial branch denervation techniques.
Endoscopic neurotomy	Neurotomy by minimal invasive (endoscopic) surgery and X-ray guided orientation, requires sedation or general anesthesia. Multiple levels can be approached by small incisions.

Table 1: Overview of different invasive treatment modalities[15-26].

a. Medial Branch Blocks

Medial branch blocks have been described in detail before, as this technique is also utilized as a diagnostic tool. As this treatment modality does not affect the pathology of the facet joints itself, it should rather be seen as a symptomatic treatment. Given the nerve innervation of the facet joints, including the dual innervation, at least a 2-level medial branch block is recommended. Both local anesthetic agents and a combination of these agents with steroids can be injected [15]. As mentioned before [16], different localizations can be chosen to achieve blockade of the medial branch (both intra- and extra-articular), and regarding the extra-articular infiltrations, different positions have been described in the literature [237,238]. Pain relief from the different techniques differs slightly, and there is no consensus in literature on the most effective injection technique. Nevertheless, a mean of 2 months of pain relief has been reported in the literature [239]. Both the intra-articular and the periarticular techniques result in an instant pain reduction that lasts for at least 1 week in a different study [240]. Regarding the duration of pain relieve it was demonstrated in a review that medial branch blocks had a better effect on short- and long-term pain relive than intra-articular blocks[17]. The substances typically used have a short-lasting effect on pain sensation. However, longer periods of pain relieve has been described upon medial branch blocks, as a combination of these interventions with physiotherapy result in improved overall results in up to 35% of patients[241].There are different agents that can be used. The local anesthetics, such as lidocaine or bupivacaine, interfere in neuronal transmission and may even affect local inflammation [18,242].The use of additional contrast agents to optimize the process of localizing the proper spot for the injections has been suggested in the literature [228].

b. Intra-articular Injection

- **<u>Steroid Injections</u>**

Prior to pain signaling, there should be pain generation, and in facetogenic pain, the substrate for pain generation is believed to be a combination of inflammation and cartilage damage. Steroids may interfere with the inflammatory local immune response and therefore play an important role in the invasive treatment of facetogenic pain. Injections of steroids into

the area of the medial branches, however, is not supposed to be very specific, and therefore, intra-articular injections are recommended. These local steroids may interfere in the nociceptive input at both the central and peripheral levels, as a part of the locally injected steroids may have a remote effect as well. Furthermore, it may modify the local immune response by impairing the pro-inflammatory mediators present in facetogenic pain patients [18]. It has been demonstrated that multilevel injections have a better outcome than single-level infiltrations, and this may either be the result of the difference between both techniques on the local level, but it has also been suggested that this is secondary to the difference in impact on the systemic immune response [243]. The success of intra-articular injections of steroids and the combination of steroids with local anesthetics has been reported in multiple studies [244,245].In a prospective randomized controlled trail with a placebo-group, however, no long-lasting pain relief has been demonstrated upon corticosteroid injections. A larger trial by the same research group found similar outcome.

- **Hyaluronic acid**

Hyaluronic acid is present in the facet joints and is an important factor in the lubrication of articular surfaces, which protects the cartilage and allows for smooth movements. As it has been described that a loss of hyaluronic acid is associated with excessive joint degeneration, additional application of this substance has also been proposed as a treatment strategy for facetogenic pain. A comparative study even demonstrated better long-term function benefit in patients with facetogenic low back pain treated by combined injection of hyaluronic acid and steroids than those patients treated with steroid injections alone [246].

- **Platelet-rich plasma**

Platelet-rich plasma intra-articular injection has been linked with two specific benefits in patients with facetogenic backpain. First it is believed to have an immune modulatory effect and secondly it may result in chondroprotection [247].Also, a combination of platelet-rich plasma and steroids or anesthetic agents has been attempted and superior outcome was reported in a comparative study with patients treated by injection of steroids/anesthetic agents only [248]. Furthermore, a systemic review on a randomized controlled trial and 2 observational studies did also show the potential benefit of augmented injections with platelet-rich plasma [249].

- **Other (experimental) agents**

In addition to the previously mentioned substances which are commonly used for intra-articular injection, there are also some less conventional agents available. Bone marrow mesenchymal stem exosomes, umbilical cord extraction agents and serapin may play a role in the treatment of facetogenic back pain in the future [18,250-252].

c. Medial Branch Radiofrequency Denervation (RFD)

In contrast to infiltrations at the level of the medial branch, radiofrequency denervation (RFD) may induce definitive damage of the medial branch. The procedure starts with the placement of electrodes at the position of the medial branch. The introduction of these electrodes is performed under imaging guidance. Thereafter, a sinusoidal current with 400-500 kHZ is produced and this leads to the generation of local heat. As a consequence, local heat generation affects the viability of nerve cells if a temperature threshold of 45^{o}C is exceeded. Cellular denaturation occurs and this prevents later nerve signaling [19,253]. Cellular denaturation requires a minimum temperature of 45^{o}C, however local temperature peaks ranging between 70 and 90^{o}Cduring the procedure have been described in the literature [254-257].Alternatively, pulsed time cycles of lower temperatures can be applied, with temperature peaks of 42^{o}C.In this case, exposure to hyperthermia is limited to 240 seconds [258]. This leads to less collateral tissue damage and is considered as a safer method. Collateral damage to both the nearby skeletal and muscular structures (leading to secondary instability) as well as to the nerve roots are prevented by pulsed techniques [169]. Literature, however has reported impaired long-term outcome with the pulsed technique, compared to conventional procedures with higher temperatures [20,259,260]. Further study on medial branch ablation underlined the essence of adequate patient selection and proper execution of the procedure, as described in International Spine Intervention Societyguidelines[261]. Just like with nerve infiltrations, adequate positioning of the electrodes is key. Propper positioning has been defined as: parallel to the target nerve to maximize denervation of the targeted nerve[178,262]. The electrodes for radiofrequency ablation result in transverse lesions around the electrodes, and minor damage to the area of the needle tip. Perpendicular placement may result in missing the optimal spot to affect the targeted nerve[20]. Follow-up study has demonstrated that up to 90% pain reduction after one year can be expected in 60 percent of patients [253]. For patients with symptomatic spondylolisthesis, comparable results have been found after 12 months of observation, with about 60% of patients experiencing80% pain relief[263]. Comparative studies found similar results in multiple spinal pathologies, with a 2–3 points difference in VAS scores between intervention and control groups [264,265]. Complication rates, however, are very low (<1%) and are limited to minor and temporary complications [266].Documented side effects after radiofrequency ablation are painful cutaneous dysesthesias or hyperesthesia, increased pain due to neuritis, neuroma formation. Motor deficits due to damage to adjacent nerves, have also been reported [267]. In order to prevent these complications, additional motor and sensory stimulatory tests can be performed prior to the neuroablation [268]. However, the need for these additional peri-interventional tests has been debated, as conventional fluoroscopically guided percutaneous radiofrequency denervation of the lumbar facets is associated with an overall 1.0% incidence of minor

complications per lesion site [266]. In addition to hyperthermic ablation, the concept of hypothermic ablation has also been tested in the past. Cooled radiofrequency, which uses internally cooled radiofrequency probes, is associated with increased lesion sizes and may result in more successful nerve denervation, but also in more collateral damage [258,269-272]. Radiofrequency denervation is a minimally invasive method and patients are typically awake during the procedure. Some sedation or local anesthesia may be offered in patients with anxiety issues [271].The size of the lesioned area depends on several parameters, such as the probe size, electrode temperature, and duration of exposure [260]. Exposure times of 60 seconds are indicated with standard-sized probes and a temperature of 90 °C [273]. However, other groups recommend exposure times of 180 seconds under these conditions [274,275].A meta-analysis of Chen et al. [276] and a systemic review from Janapala et al. [277] on patients with facetogenic chronic LBP demonstrated the feasibility and safety of medial branch radiofrequency ablation. Another systematic review of a total of four studies, comparing sham, placebo and radiofrequency ablation groups revealed conflicting results when focusing on the three to six months follow-up [278].Less positive research results are from a retrospective study from Starr et al. on about 45,000 patients in which 33.1% of patients required a second intervention for remaining pain symptoms[279]. In addition, Juch et al. [280] summed up the results of three randomized controlled trials on patients with facet joint related back pain in which radiofrequency ablation therapies did not result in improved outcome compared with control groups [280,281]. A combination of radiofrequency ablation and corticosteroid injections for facetogenic low back pain was also investigated in a prospective observational study. In 82 participants, only 6% of patients required a second radiofrequency ablation after 2 years of follow-up [282].

d. Capsule Radiofrequency Denervation

As an alternative to the medial branch denervation technique, intra-articular radiofrequency and a modified technique in which the multifidus is spared have also been described [283].The outcomes of these intra-articular ablation techniques are comparable to conventional medial branch ablations regarding efficiency and safety. Pulsed modifications, as described for medial branch ablations are associated with a better long-term effect than continuous capsule ablation[21].Again, a combination of different treatment strategies may also be beneficial, as in patients with lumbar facet cysts, coagulation of both the capsule and the medial branch leads to superior pain relief[284]. A clinical study by Chang et al.[285] on patients with facetogenic pain only revealed that in 10 out of 20 patients had significant pain relief at six months after intra-articular pulsed radiofrequency ablation. A study by Do et al.[286] found similar results six months after intervention.

e. Cryoneurolysis (CN)

In contrast to hyperthermic ablation techniques, cryoneurolysis has also been attempted. It has been demonstrated that the application of cold also leads to nerve denaturation. Cryoneurolysis is the application of cold to the nerve to cause its denaturation. Local hypothermia is produced by the rapid decompression of gases (N_2O or CO_2) at the end of a cryoprobe. This results in a prompt temperature drop to -70 °C [268]. A minimum of -20 °C has been calculated to achieve a blockage of nerve fibres to stop conducting however longer-term blockage requires denaturation of the nerves [268].

As with hyperthermic ablation techniques, success rates highly rely on patient selection and these are in line with recommendations for radiofrequency ablation as described by the International Spine Intervention Society [261]. Different variables dictate the success of the intervention and the degree of cold, the contact surface and the duration of exposure are to be considered [287].In contrast to RFD, a tangential approach of the probe is not required to achieve proper temperature alterations at the tissue site because a local ice conglomerate results in a wide-spread and equal temperature distribution at the tip [288]. Several research groups support the use of cryotherapy, as they believe it produces better outcomes than alternative methods of neurolysis and results in less periprocedural pain [288,289]. However, the long-term outcome data are unclear. It has been suggested that cryo-augmented techniques may be less accurate than conventional RFD. Three prospective studies [237,290,291] demonstrated pain reduction for a duration of 50% over six months, and similar data came from a retrospective study by Wolter et al. [289]. Advocates of cryoneurolysis mention the following benefits of this technique: less tissue damage, less risk of neuroma or neuritis, and a larger denervation area at the needle tip[289,292].

Nerve fibers stop conducting at-20 C°, so ice-cold temperatures created by cryoneurolysis procedure induce a conduction block. The patient's pain is tolerable. Additional work from Kastler et al. [293] showed that the improvement in patients with facetogenic backpain undergoing the intervention, was maintained in 77% of cases after 12 months of follow-up.

f. Chemical Neurolysis

Chemical neurolysis, does not require temporary changes in local temperature to alter local cell homeostasis, but achieves the same effect by the local administration of chemical substances. These chemical substances achieve pain relieve by denaturing of nerves [22]. Variables affecting the impact on nerves and the lesion size include the type of the agent and neurolysis techniques are able to create a larger and more thorough lesion compared to a radiofrequency neurolysis [294].

Three agents are most frequently used for this treatment: alcohol, phenol and glycerol [295]. Major disadvantages of this technique have been described, however. These include: local necrosis of surrounding tissue, neuritis, neuroma formation and uncontrolled diffusion with

marked collateral damage. Additionally, paradox hyperalgesia has also been reported. These cases are related to damage to axonal membranes and related overstimulation. These incidents have been reported either directly after the intervention or many months later [296]. For alcohol neurolysis, a neurolytic effect has been described at concentrations of ethyl alcohol exceeding 50%, although in order to achieve permanent neurolysis concentrations exceeding 95% are most frequently recommended [157].Alcohol is associated with a higher rate of neuritis than phenol [297]. Neurolysis with Phenol is also concentration-dependent, and a 3% phenol concentration is associated with a comparable neurolytic effect as 40% alcohol (in saline). Phenol causes a transient local anesthesia that lasts for four to five months. A benefit of Phenol is its low potential of diffusion and low rates of periprocedural pain increases compared to other techniques [157]. Glycerol has been adopted as treatment modality for back pain from the field of ear-nose-throat medicine [298,299]. In this field glycerol has been utilized to treat facial nerve pain syndromes. Interestingly, pain improved, whereas facial sensation remained intact upon local infiltration of glycerol [300,301]. Glycerol, which is structurally related to ethanol [302]was thereafter also introduced for facetogenic pain. However, there are currently no controlled prospective studies or long-term follow-up available.

g. Dorsal Root Neurotomy

The dorsal root further transmits signals from the medial branch nerve to the brain, and dorsal root neurotomy is considered as a more radical intervention than medial branch aimed procedures. A long-term comparative study demonstrated that patients exposed to dorsal root neurotomy had better pain scores after 2 years than patients treated with medial branch neurotomy [21].Another study of 50 participants showed that patients treated with percutaneous dorsal root neurotomy had a 100% pain relief even after 2 years of post-interventional observation [23]. Dorsal ramus neurotomy at the L5 level had significantly better and longer lasting pain reduction than medial branch blocks in another study as well. For this study a total of 326 patients were investigated, of whom 99 patients were treated with dorsal ramus neurotomy, and 227 received a lumbar radiofrequency neurotomy. In the patients treated with dorsal ramus neurotomy, the pain relief at 6 and 12 months of follow-up was significantly better than that reported in their counterparts treated by medial branch neurotomy (respectively: 99 vs. 74% and 79 vs 65%) [24]. These studies suggest that dorsal root neurotomy may be a more effective treatment for low back pain than medial branch neurotomy. Therefore, dorsal ramus block therapy could be a more effective treatment than interventions aimed to block the medial branch.

h. Endoscopic neurotomy

Endoscopic interventions have gained popularity in different fields of medicine and have been introduced into spine surgery over the last few decades. Endoscopic neurotomy, which allows for exploration of the transverse process and thereby a more widespread area of ligation has also been implemented in spine surgery recently [25]. Exploration of the transverse process enables widespread exposure of the medial branch, which innervates the facet joint. Direct visualization of the nerve enables the physician to determine the perfect spot for ablation, even in cases of aberrant innervation such as in anatomical variations [26].

As with medial branch blocks, it is well known that two nerves need to be transected to denervate a lumbar facet joint. In medial branch blocks, the destruction of the nerve structures cannot be confirmed visually. This makes it tempting to hypothesize that endoscopic neurotomy is superior to medial branch blocks. Given the minimal collateral tissue damage due to the endoscopic approach to the spine, this technique may also be favored over interventional neurotomy surgery, in which a cut-down to the bone is required [26,303].

A comparative study on 55 patients with facetogenic low back pain by Du et al. revealed that those patients treated with endoscopic neurotomy had a better long-term outcome than a control group with radiofrequency neurotomy [303]. Specifically, in this study, 36 patients underwent radiofrequency ablation and 19 patients were selected for endoscopic neurotomy. It is was shown that pain reduction was achieved in both groups, however, increased pain reduction was reported after 6 and 12 months in those patients treated with endoscopy neurotomy, compared to radiofrequency ablation [303]. Based on a study from Melonceli and co-workers, pain relief upon endoscopic neurotomy lasts for 2 years in the majority of patients [23]. Of note, randomization was not applied. Song et al. revealed prolonged effectiveness of neurotomy by endoscopic approaches than by radiofrequency [304]. A study by Xue et al. further reported better outcome with endoscopic neurotomy than after medial branch radiofrequency, with the authors believing that this is due to the improved accuracy of the denervation through direct visualization [305].

A randomized controlled study comparing endoscopic and radiofrequency neurotomy showed pain reduction in both interventions. Pain relief faded within 12 months in the radiofrequency cohort, whereas prolonged pain reduction occurred in patients treated by endoscopic neurotomy [306]. Similar findings were published by Walter et al. [307].

3. Research question and study-hypothesis

It is a dilemma when it comes to the recurrence of facet joint pain after successful medial branch blocks or intra-articular blocks with steroids, especially in patients with cardiac implantable electronic devices (CIEDs). Another problem faced by spine specialists is the recurrence of pain after initial or repeated radiofrequency denervation treatment of the medial branch of the posterior ramus, which generally prompts the search for alternative ablation methods that provide longer-lasting pain relief.

RFD aims to dampen noxious neural transmission and is considered as an established, minimally invasive treatment for chronic low back pain. Its effectiveness has been demonstrated in several clinical studies [256,264,308-311].Given the total number of annual implantations of implantable electronic cardiac devices, including pacemakers, implanted cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy devices (CRTDs), this patient population is significant. In addition, this patient population will continue to grow over the next decade as a result of improved technology and increased life expectancy [312]. As a consequence, the population of patients with CIEDs and treatment-requiring low back pain, will grow as well.

The electrical currents used in the RFD generate electromagnetic interference (EMI) which can result in unintended energy transfer to implanted devices. This could potentially affect device function or damage the device [313-315]. Although there have been no reported cases of cardiac implantable electronic devices (CIEDs) malfunctioning following RFD and resulting in serious injury or death, interference and inappropriate shocks may occur [316]. According to the guidelines from the American Society of Pain and Neuroscience (ASPN), evidence on the utilization of RFD in individuals with CIEDs is limited to case reports (Grade B, moderate certainty) and additional high-quality studies are warranted [317].

The growing population of elderly patients with implanted cardiac implantable electronic devices (CIEDs) is prompting a search for alternative denervation and ablation methods to avoid potential interference with device function or damage to the device. Chemical neurolysis using ethyl alcohol 95% or glycerol 20% may be a solution for RFD when safety is assured.

The study utilizes the Visual Analog Scale (VAS) and the Core Outcome Measures Index for the back (COMI-back) to measure outcome parameters at various time points throughout the study. VAS assess pain level [35] and COMI-back is a brief and validated instrument for assessing the main outcomes in patients with back problems, including pain, function, symptom-related well-being, quality of life, and overall disability [36].

Study-hypothesis

- **H0:** There are no differences.

- **H0.1**: There are no differences over time.
- **H0.2**: Interaction effects between Time * Group are not significant.
- **H0.3**: Effects between groups are not significant.

- **H1:** There are differences.

- **H1.1:** Over time, patients experience improvement (reduction in pain, increase in quality of life). Pain was scored on an 11-point scale, with 0 being pain-free and 10 being the maximum possible pain. After starting treatment, we expect VAS scores to decrease. The Core Outcome Measures Index (COMI-back) can range from 0 to 10, with 0 indicating no impairment and 10 representing maximum impairment. We expect COMI scores to decrease after treatment initiation.
- **H1.2:** Interaction effects between Time * Group are significant. This indicates that the treatment methods have varying effects on dependent variables (COMI and VAS) over time.
- **H1.3:** Effects between groups = Group comparison. H1 or alternative hypothesis: The groups benefit differently from the treatment (VAS and COMI-back).

Therefore, the aim of the current study is to compare the effects of RFD and chemical neurolysis (with ethyl alcohol 95% or glycerol 20%) and to determine both the short- and medium-term clinical outcomes of different types of neurolysis.

4. Material and Methods

4.1 Study design and ethical approval

A prospective cohort study was performed at the Department of Spine Surgery at our institution, an accredited spine center certified by the German Spine Society (DWG) and the EUROSPINE Society. Patients were enrolled in the study between 01.12.2017 and 01.12.2019. The regional Ethics Committee approved the protocol (file number: 2016448). Informed consent was obtained from all the participants prior to the administration of the different injection therapies.

4.2 Cohorts

This study focuses on adult patients with recurrent chronic lumbar pain despite maximal conservative therapy, including oral analgesics, physiotherapy and lifestyle modification. The study aims to identify candidates for facet neurolysis based on specific inclusion criteria:

I. To be eligible for the study, participants must be 18 years or older and have a confirmed history of recurrent chronic lumbar facetogenic pain that has limited their function for at least six months. Additionally, they must have failed maximal conservative therapy.

II. In order to diagnose degenerative facet pathology, it is chief to report the presence of paraspinal tenderness and increased pain upon hyperextension, rotation or lateral bending of the lower lumbar spine and absence of radicular symptoms.

III. To exclude alternative diagnoses and confirm findings reflecting degenerative facet pathology, all patients underwent routine lumbar spine MRI.

IV. A short-term reduction of at least 50% on the Visual Analogue Scale (VAS) must be observed after infiltrations of Medial Branch Blocks with a mixture of 10 mL of 2% ropivacaine hydrochloride (20 mg/10 mL) (Ratiopharm GmbH, Ulm, Germany) and 1 mL triamcinolone acetonide 40 mg (Hexal AG, Holzkirchen, Germany) in the lumbar facet joints L3/L4-L5/S1.

The following specific additional exclusion criteria were utilised:

Confirmed concurrent disc herniation, symptomatic radiculopathies, spinal instability, vertebral fractures, rheumatic disorders, neuromuscular disorders, history of opioid abuse, pregnancy, lactation, a history of adverse reactions to glycerol or ethyl alcohol, or if written informed consent was not obtained.

4.3 Execution of diagnostic medial branch blocks

All of the injections were performed in the prone position and under intermittent fluoroscopic visualisation (OEC Fluorstar, GE Healthcare, Chicago, IL, USA) with continuous monitoring of the patients' vital signs (saturation and pulse rate) and frequent blood pressure measurements. X-ray imaging was conducted by an experienced technician.

Briefly, tender lumbar facet joints (L3/L4–L5/S1) were palpated, marked, and located with fluoroscopic guidance. Under aseptic conditions, a 22-G needle was inserted until bone was contacted at the edge of the facet joint. Adequate needle positioning was confirmed by fluoroscopy. When the needle was in place, 0.5–1.5 mL of a mixture of 10 mL of 2% ropivacaine and 1 mL of triamcinolone 40 mg was injected into the target joints L3/L4–L5/S1. Consequently, the following facet joints were infiltrated bilaterally in all participants: L3/L4, L4/L5, L5/S1. Selective infiltrations of specific joints were not performed. Afterwards, the injection site was disinfected again and covered with a plaster.

4.4 Enrolment procedure and grouping procedure

Following the administration of the diagnostic medial branch blockage and the recurrence of lumbar facet joint pain, the patients who were considered to be candidates were assessed to determine if they met the inclusion or exclusion criteria.

After being provided with sufficient information regarding treatment options, all the patients were provided with written informed consent documents listing the actual diagnosis and an overview of the treatment options (including conservative options) and potential complications. The patients were offered three treatment options, and they were allowed to select the treatment modality they preferred. They were then treated and grouped in accordance with that decision, as follows:

The Gly-20 Group: Chemical neurolysis with glycerol 20%

The EA-95Group: Chemical neurolysis with ethyl alcohol 95%

The RFD Group: Radiofrequency denervation

Patients were free to obtain a second opinion or to discuss the proposed treatment options with their general practitioner. Once the decision-making process had been completed and informed consent had been obtained, patients were scheduled to undergo the intervention and a pre-interventional assessment was carried out. Patient enrolment is displayed in Figure 11.

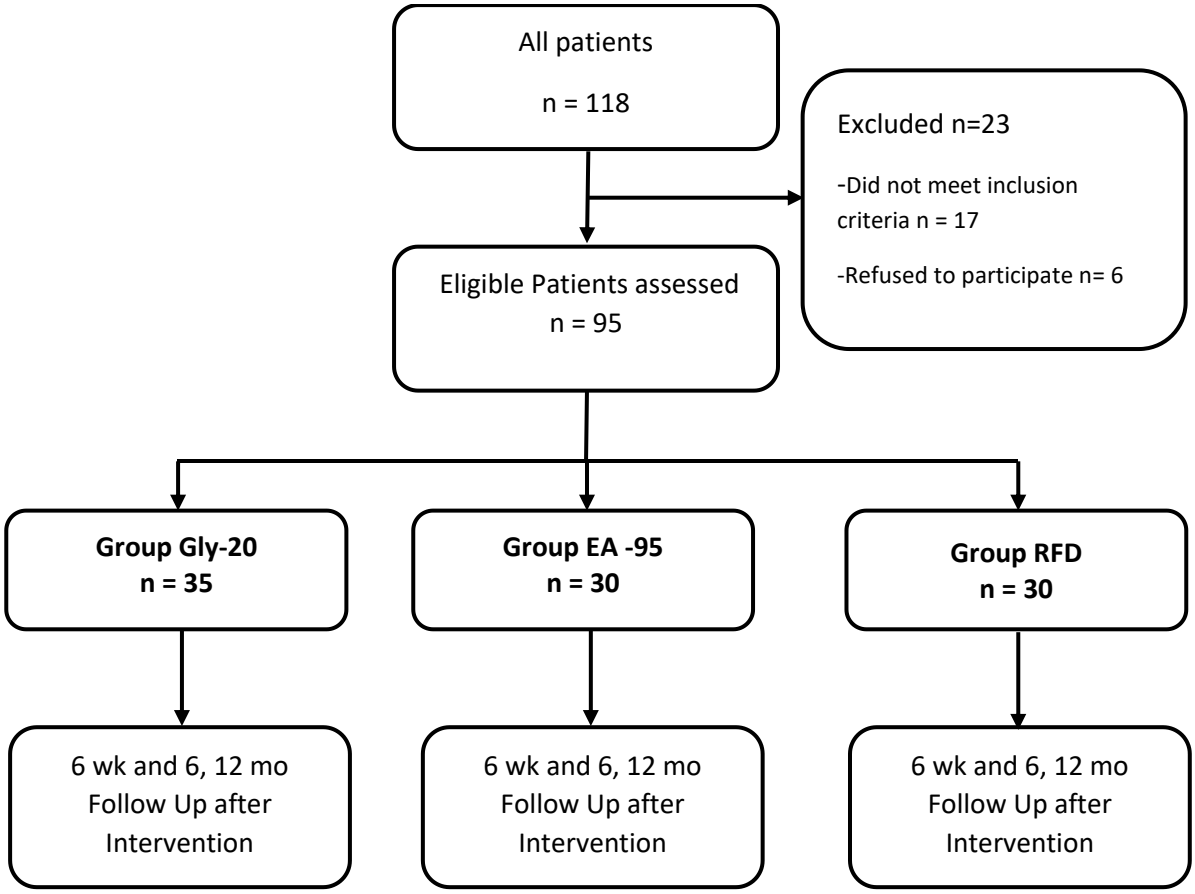

Figure 11: Flowchart: Overview of patient enrolment, grouping and follow-up.

4.5 Execution of radiofrequency denervation

The participants were placed in a prone position; all injections were performed under intermittent fluoroscopic visualization and their vital signs were continuously monitored. Figure 12 displays the setup. Electrodes and disposable 22-G curved radiofrequency needles with 100-mm active tips (Neuro-Therm, Wilmington, MA, USA) were placed at the site of the medial branch of the dorsal ramus of the relevant L3/4–L5/S1 facet joints. A representative example of needle placement is attached as Figure 13. Correct placement was confirmed using electrostimulation in the sensory testing mode (50 Hz, 0-1V) and by the motor testing mode (2 Hz, 1-10V), ramped up to at least double the sensory stimulation, value with a minimum of 3V. Then, 1 mL of 2% ropivacaine was injected through the cannula. The radiofrequency electrode was then reinserted into the cannula and the lesion was made at a temperature of 80°C for 90 seconds using a radiofrequency generator (Electrothermal 20S Spine System, Smith & Nephew, London, GB). Selective denervation of specific facet joints was not performed. The following facet joints were denervated bilaterally in all participants: L3/L4, L4/L5, L5/S1.

4.6 Execution of chemical neurolysis with ethyl alcohol 95%

The same setup was used for the steroid infiltration and RFD. After positioning the 22-G needle at the junction of the superior articular process and the transverse process of the target vertebrae, the upper outer quadrant of the pedicle, L5 dorsal ramus, the same needle was used to strike the junction of the superior medial sacral ala, just lateral to the superior articular process of S1 under fluoroscopy. Needle placement was ensured from the anteroposterior and lateral viewpoint. When the needle was in place, 0.5–1 mL of 2% ropivacaine was used to obtain a sufficient analgesic effect and to ensure that the position of the needle tip was not near the ventral ramus. Prior to the ethyl alcohol injection, each patient was asked about radicular pain or traction of the leg, which indicated incorrect placement of the needle, and the bevel opening was directed caudally to avoid spread of the injectate into the intervertebral foramen. The preferable volume of the ethyl alcohol 95% solution (B. Braun, Melsungen, Germany) should be between 1–1.5 mL at each injection site. According to our guidelines, 0.5 mL of the solution was injected once during a time frame of 30 seconds in order to avoid unwanted spread. Prior to the injection, the solution was stored in accordance with the recommendations from the manufacturer at 4^{o}C and under dark conditions. Again, we did not perform selective denervation of specific facet joints. In all patients, the following facet joints were denervated bilaterally: L3/L4, L4/L5, L5/S1.

4.7 Execution of chemical neurolysis with glycerol 20%

The setting for glycerol 20% neurolysis was the same as the one used for ethyl alcohol 95%. Based on recommendations from the literature and our own experience, we used glycerol 20% (glycerol anhydricum 3.0 g/15mL produced at our institution). Prior to the injection, glycerol 20% was stored at 4^{o}C and under dark conditions.

In our institution, a total of 1.000 patients are treated annually using different types of X-rays controlled semi-invasive infiltration therapies. All the procedures are performed by experienced specialists with extensive experience in the field of pain management (> 500 injections) and spinal surgery. Selective denervation of specific facet joints was not performed. In all patients the following joints were denervated bilaterally: L3/L4, L4/L5, L5/S1.

Figure 12: Example of patient positioning, set-up of materials, imaging, and monitoring tools.

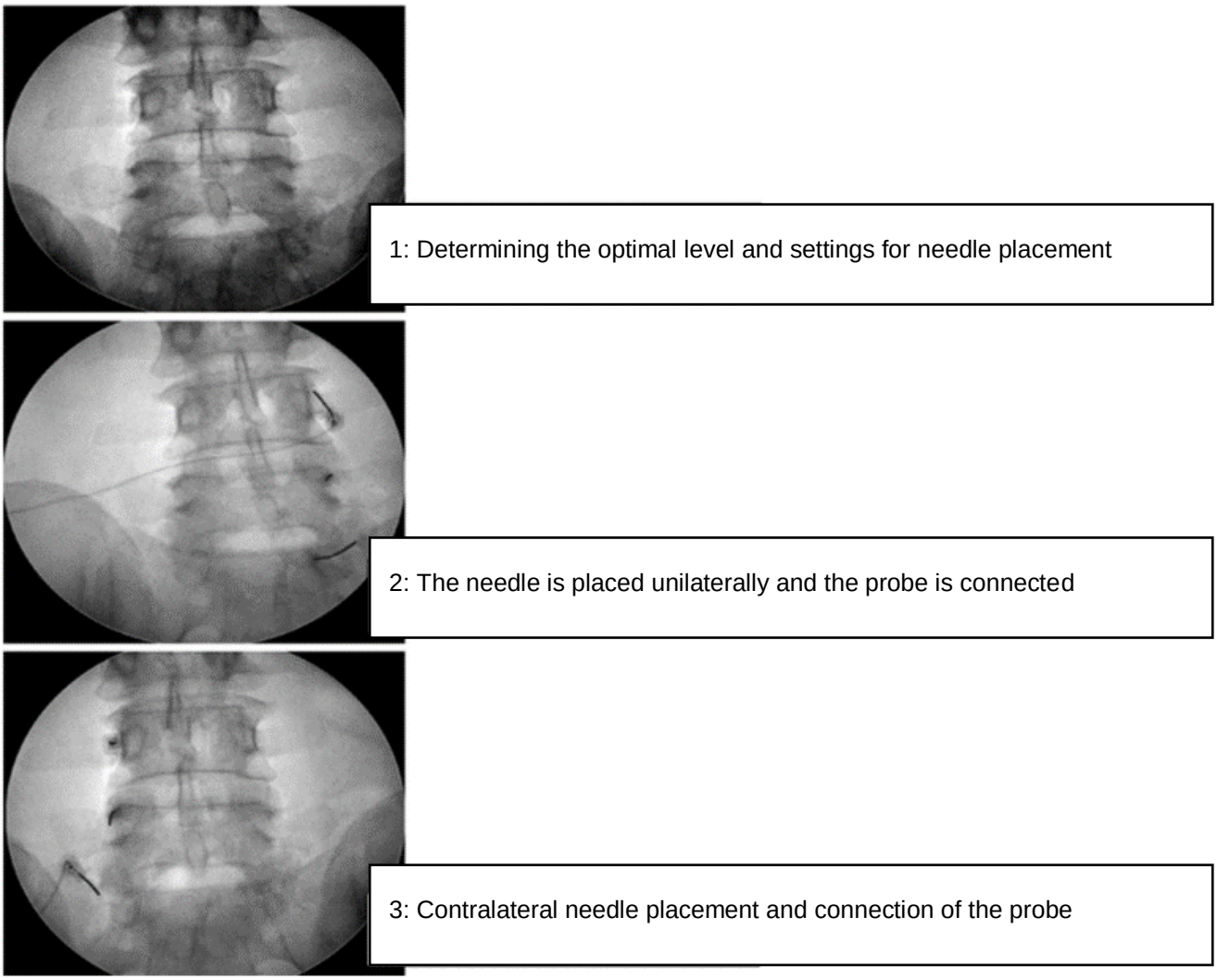

Figure 13: Representative example of intra-interventional imaging: examples of x-ray-guided needle positioning.

4.8 Outcome parameters

The following outcome parameters were used, based on information from the German Spine Database of the German Spine Society (DWG-Registry):

Patient characteristics: gender, age, date of presentation, date of intervention

Pain characteristics: VAS, the Core Outcome Measures Index for the back (COMI-back).

4.8.1. Visual Analog Scale (VAS):

Pain was assessed using an 11-point numeric rating scale, where zero represents the absence of pain and 10 represents the most intense pain possible [35].

4.8.2. The Core Outcome Measures Index (COMI)-back:

A brief instrument for assessing main outcome in patients with back problems (pain, function, symptom-related well-being, quality of life and overall disability) [36]. The COMI-back was developed during the ´Spine Tango´ project and is a validated outcome assessment tool for patients with back problems. A higher COMI-back represents inferior outcome [318].

4.8.3. Additional outcome data

Additional outcome data: all Complications, subsequent operative interventions, and re-hospitalization were documented, observed, and evaluated.

4.9 Statistical methods

Statistical analysis was performed using IBM SPSS Statistics for Windows 22.0 (Chicago, IL, USA). The differences between the groups were calculated with Analysis of Variance for repeated Measurements (rmANOVA). The Greenhouse-Geisser correction is used when the assumption of sphericity is violated. Post-hoc analysis was calculated by Tukey-Kramer Test. Chi-square or Fisher's exact test for the ordinal data and T-test or the Mann-Whitney U test for the continuous data. P-values< 0.05 were considered to be statistically significant.

The qualitative demographic variables (e.g. gender) are summarized using absolute and percentage values and the quantitative demographic data (e.g. age) are presented using mean, minimum, maximum, standard deviation and median.

Post hoc analysis was used to identify specific group differences and multiple group comparisons were performed using the Tukey-Kramer test, in the case significant effects between groups were observed.

5. Results

5.1 Patient inclusion and baseline data

During the inclusion period, lumbar facet denervation was administered to 118 patients. However, 23 of them were excluded as they did not meet the defined criteria. Eventually, 95 patients were eligible for the study. Out of these, 35 received glycerol injection therapy, 30 opted for RFD, and 30 preferred ethyl alcohol injection therapy. The flowchart in Figure 11 provides a summary of patient inclusion and grouping.

Prior to the intervention, there were no statistically significant differences in baseline parameters observed among the three groups. Table 2 summarises the baseline characteristics. Gender comparisons were performed using chi-squared tests. while age comparisons, VAS, and COMI-back comparisons were performed using Analysis of Variance for Repeated Measurements (rmANOVA).

Variable	Group Gly-20	Group EA-95	Group RFD	Total
Age (years)	62.3 ± 11.5	65.6 ± 12.7	63.3 ± 16.1	63.7 ± 13.4
Gender				
Female	26 (74%)	16 (53%)	18 (60%)	60 (63%)
Male	9 (26%)	14 (47%)	12(40%)	35 (37%)
VAS	8.14 ± 1.26	7.87 ± 2.01	8.00 ± 1.46	8.01 ± 1.58
COMI-back	8.45 ± 1.46	8.02 ± 1.55	8.45 ± 0.94	8.31 ± 1.35

Table 2:Patient characteristics and baseline parameters.

5.1.1. Age

The overall mean age was 63.7 years (standard deviation: 13.4 years). The youngest patient in the dataset was 25 years old, while the oldest patient was 86 years old. Figure 14 illustrates the distribution of individuals across different age groups. The EA-95 group tends to be older on average, while the Gly-20 and RFD groups have comparable mean ages. However, no statistically significant age differences were found between the three treatment groups ($F=0.517$; $df=2/92$; $p=0.598$).

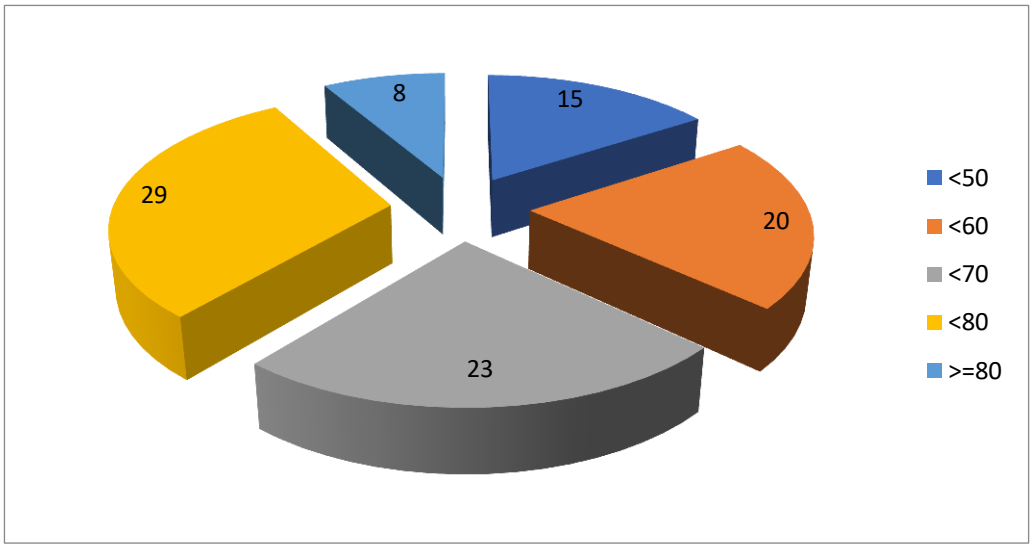

Figure 14: Distribution of study population in different age groups.

5.1.2. Gender

Overall, the entire dataset contains more female patients (n=60) than male patients (n=30).Figure 15 illustrates the overall gender distribution of the study population. No statistically significant differences in gender distribution were found between the different study conditions (Chi^2=3.326; df=2; p=0.198).

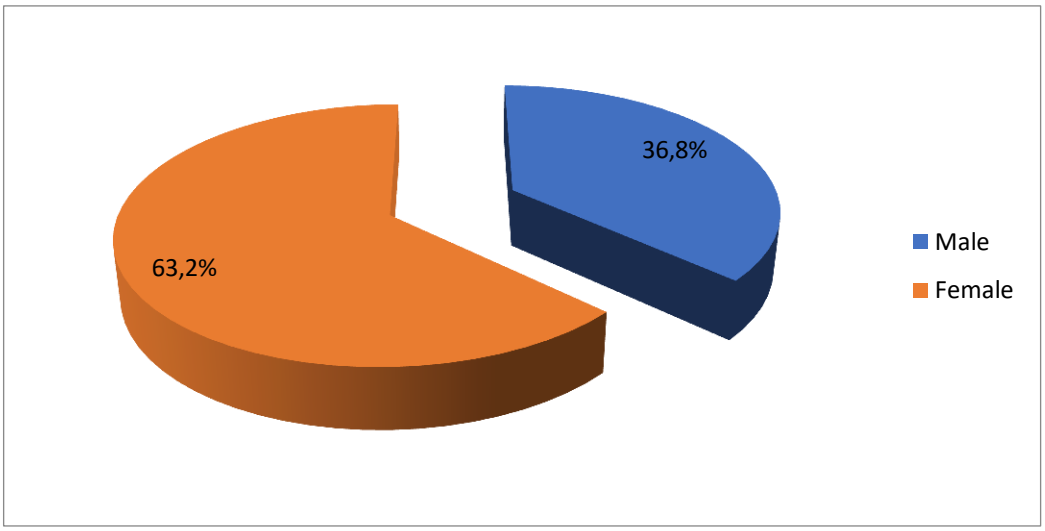

Figure 15: Overall gender distribution of the study population.

5.1.3. Preinterventional VAS

Furthermore, an overall mean VAS (prior to intervention) of 8.01 (standard deviation: 1.58) was reported by the patients. Figure 14 illustrates the Mean VAS in the different study groups before the intervention. The Gly-20 group has the highest average (Mx=8.14; SD=1.264) VAS score, whereas the EA-95 group has lowest mean but highest variability of VAS-scores (Mx=7,87; SD=2.031). RFD score is between the two (Mx=8.0; SD=1.462). Prior to intervention, there were no significant differences between the three groups (F=0.243; df=2/92; p=0.784). Figure 14 illustrates the Mean VAS and the 95% confidence interval in the different study groups before the intervention.

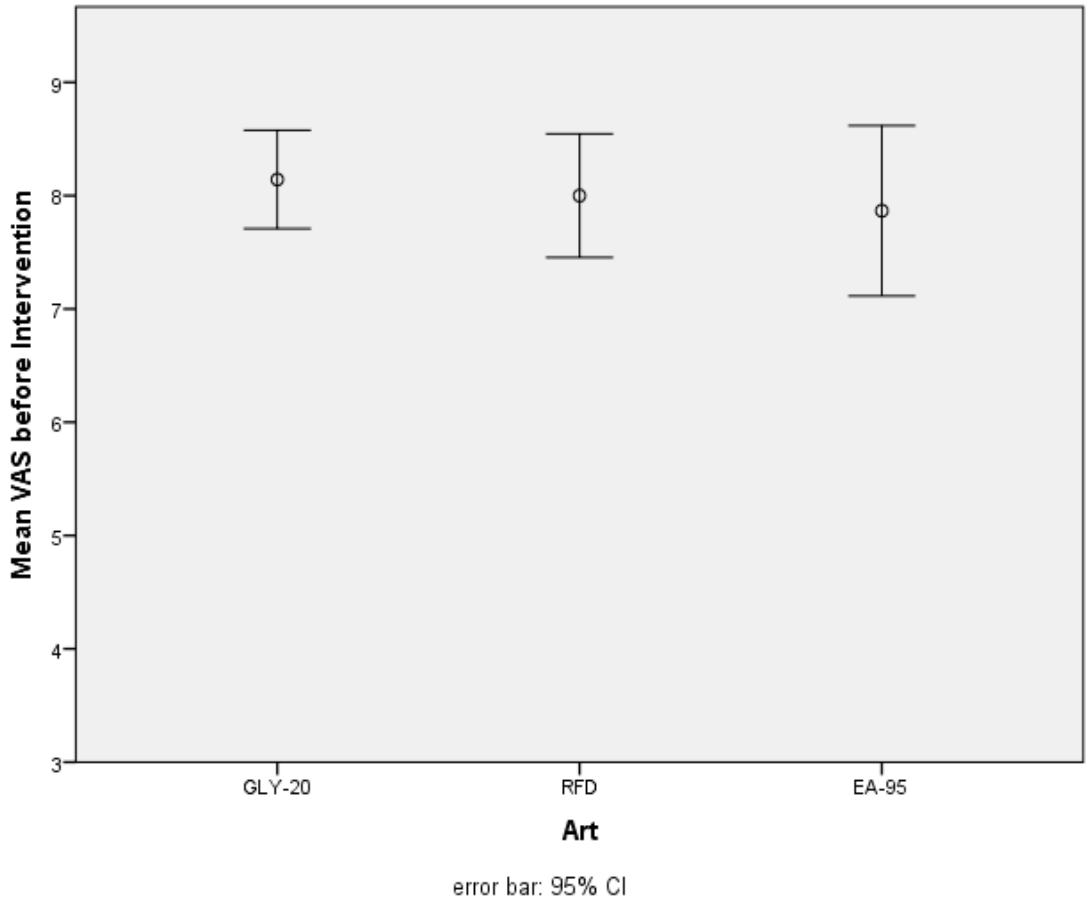

Figure 16*:* Mean VAS in the different study groups before the intervention

5.1.4. Preinterventional COMI

The overall mean COMI-back score is 8.31 (standard deviation:1.35). Figure 14 illustrates the Mean COMI and the 95% confidence interval in the different study groups before the intervention. More specifically, the Gly-20 (Mx=8.447; SD=1.463) and RFD (Mx=8.450; SD=0.936) groups have similar average COMI-back scores, while there was a non-statistically significant trend towards lower mean COMI-back scores in the EA-95 group

(Mx=8.022; SD=1.553). There were no statistically significant differences in COMI-back scores between groups (F=1.015; df=2/92; p=0.367).

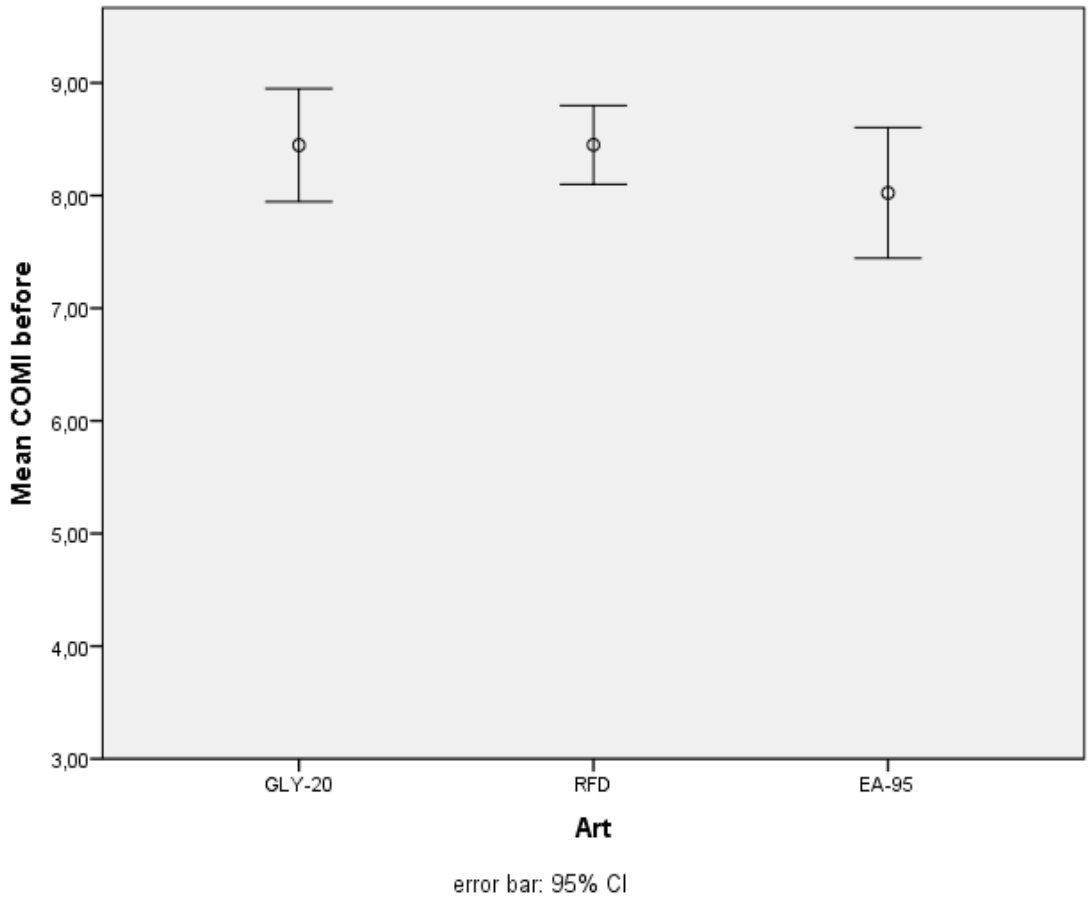

Figure 17: Mean COMI in the different study groups before the intervention

5.2 Short-term outcome parameters

5.2.1. VAS outcomes over 6 months

Repeated measurement analysis of variance (rmANOVA) was performed to determine whether there was any difference between the 3 different management groups (Gly-20, RFD and EA-95). dependent variables were the VAS scores over 6 months.

Assumptions of normality, homogeneity of variance-covariance matrices [the Box's M test of 0.992 indicates homogeneity of covariance matrices between groups (p=0.748)], linearity and multicollinearity were satisfied. Tests of between-subjects effects show that the independent variables (Gly-20, RFD and EA-95) have a significant effect on the dependent variable (VAS over 6 months) [F=4.68; df=2/70; p=0.012]. Pain (VAS) was significantly lower after every intervention during the observation period of six months [F=41.75; df=2/140; p<0.001]. Figure 14 illustrates the total estimated marginal means of VAS over six months.

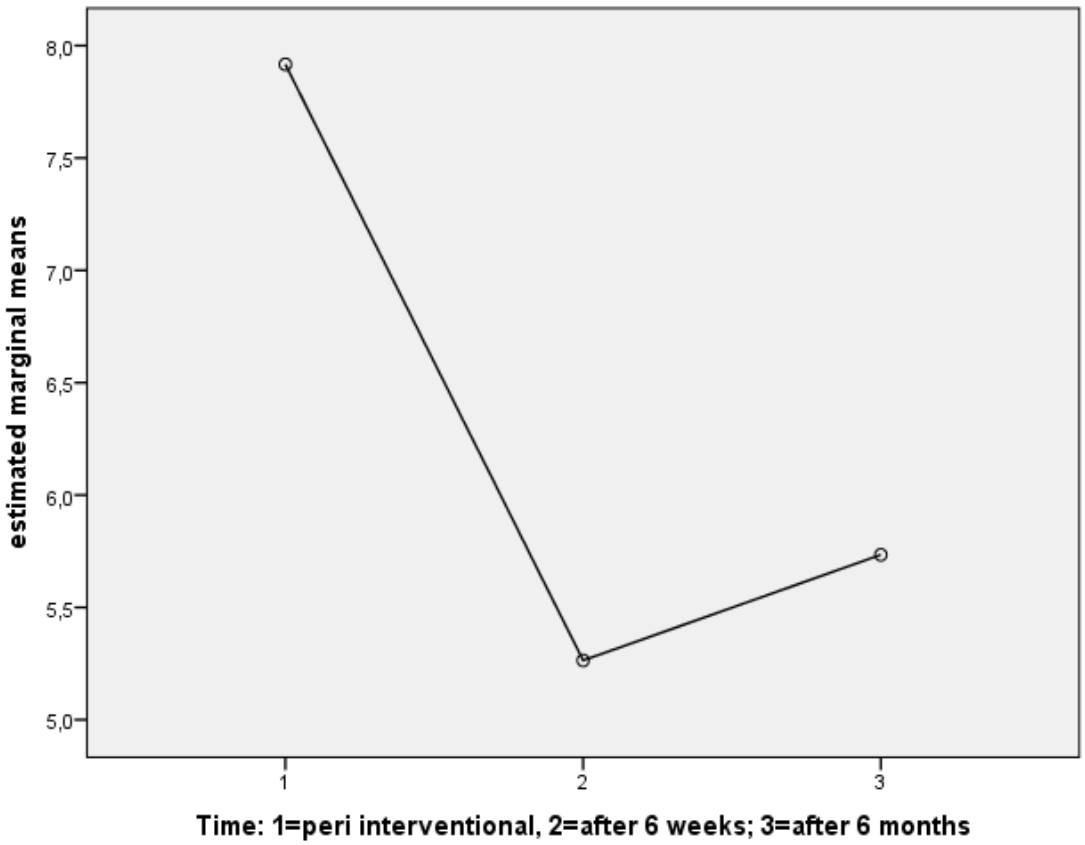

Figure 18: The Total estimated marginal means of VAS over six months

A significant interaction effect time by group [F=2.76; df=4/140; p=0.030] indicates that pain changed differently over time, in the three treatment groups. Table 3 shows multiple comparisons between the three different management groups (Gly-20, RFD and EA-95) and compares the mean differences of pain between the different groups. Figure 19 visualizes

estimated marginal means of VAS over 6 months by means between the three different Treatments Groups. In addition, the post-hoc analysis (Tukey-Kramer test) showed that the significant difference was between the Gly-20 group and the RFD group (p=0.012).

dependent variable	Art (I)	Art (J)	Mean Difference (I- J)	Std. Error	Sig.	95 % Confidence Interval	
						Lower Bound	Upper Bound
VAS over 6 months	Gly-20	RFD	1.66*	.560	.012	0.32	3.00
		EA-95	0.36	.581	.813	-1.03	1.75
	RFD	Gly-20	-1.66*	.560	.012	-3.00	-0.32
		EA-95	-1.30	.602	.085	-2.74	0.14
	EA-95	Gly-20	-0.36	.581	.813	-1.75	1.03
		RFD	1.30	.602	.085	-0.14	2.74

Based on observed means

The error term is Mean Square (Error)= 4.053

*. The mean difference is significant at the .05 level

The post hoc analysis (Tukey-Kramer test) showed that there was a difference between the Gly-20 and RFD groups (p=0.012).

Table 3: Multiple Comparisons by Post-Hoc analysis (Tukey-Kramer Test) between VAS over 6 months.

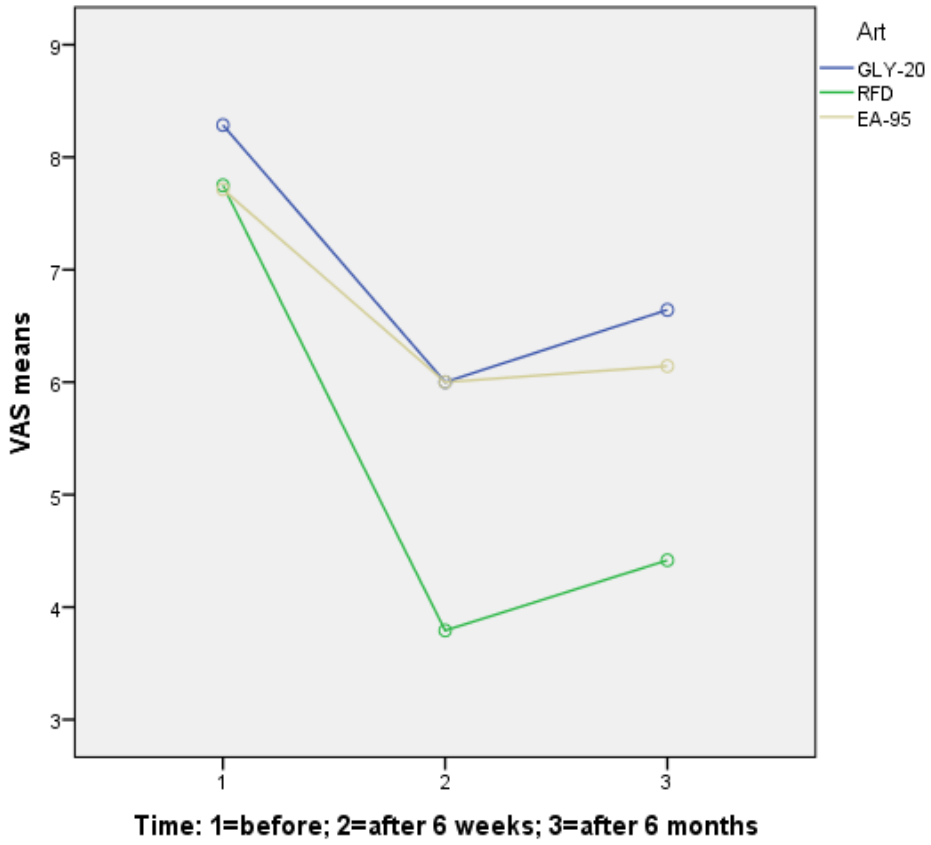

Figure 19: Estimated marginal mean of the VAS of the different treatment groups over 6 months

5.2.2. COMI-back outcomes over 6 months

A repeated measurement analysis of variance (rmANOVA) was conducted to determine if there was a difference in Quality of Life among the three different treatment groups (Gly-20, RFD, and EA-95). The measures of COMI-back over 6 months are the dependent variables. Assumptions of normality, homogeneity of variance-covariance matrices [the Box's M test of 0.0986 indicates homogeneity of covariance matrices between groups (p=0.625)], linearity and multicollinearity were satisfied. The effect of treatment on Quality of Life over six-months period is significant [F=26.59; df=2/140; p<0.001]. Figure 14 illustrates the total estimated marginal means of COMI-back over six months.

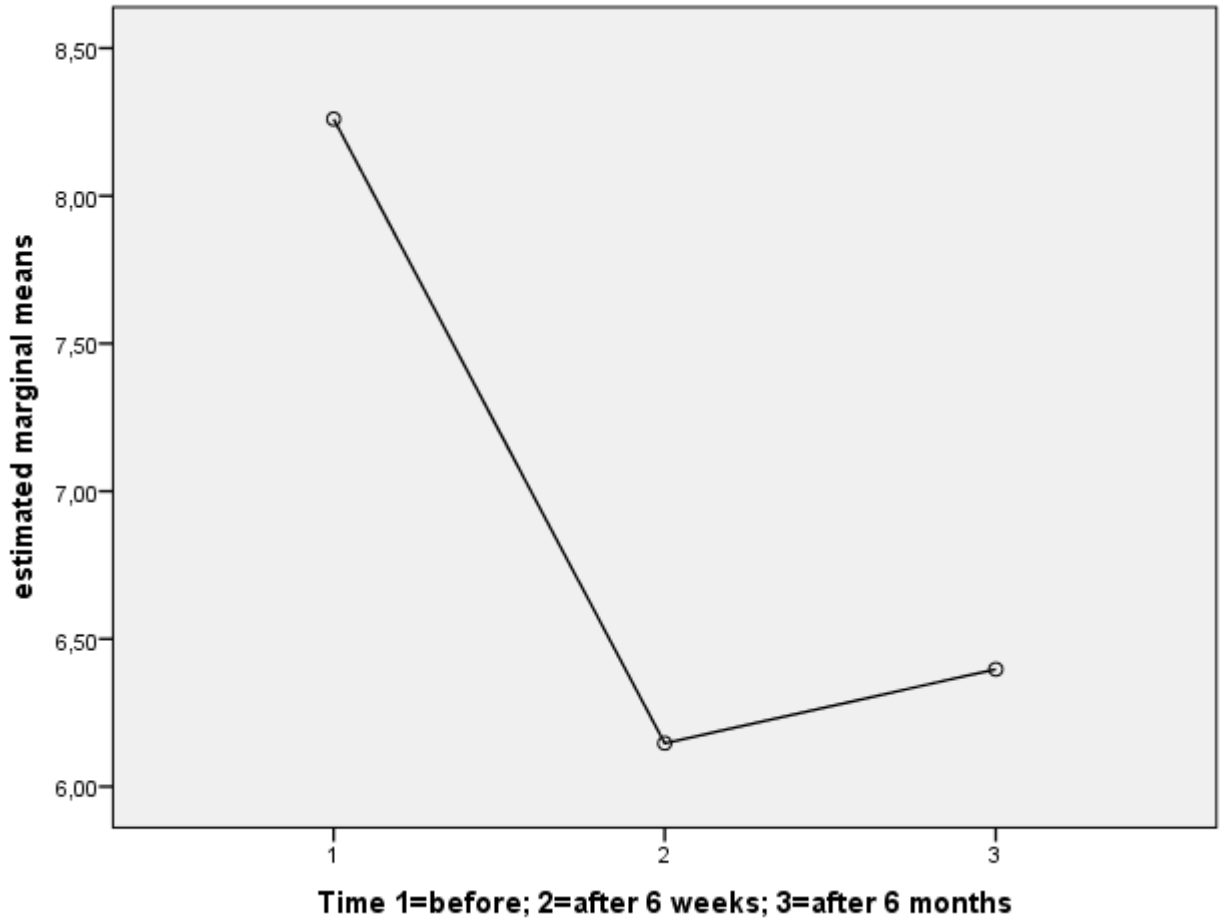

Figure 20: The total estimated marginal means of COMI-back over six months.

An interaction effect time by group is also significant [F=3.18; df=4/140; p=0.016]. Tests of between-subjects effects show that the independent variables (Gly-20, RFD and EA-95) have no different effect on Quality of Life (COMI-back over 6 months) [F=2.89; df=2/70; p=0.062].

Table 4 demonstrates multiple comparisons between the three different treatment groups (Gly-20, RFD and EA-95) and compares the differences in mean COMI-back over 6 months. The post-hoc analysis (Tukey-Kramer test) showed that there was a difference between the

Gly- 20 group and the RFD group (p=0.049) which, however, should not be overinterpreted due to the non-significant rmANOVA. Figure 21 visualized the estimated marginal means of COMI-back of the different Treatments groups over 6 months by the plots generated by SPSS Program.

dependent variable	Art (I)	Art (J)	Mean Difference (I- J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
COMI over 6 months	Gly-20	RFD	1.3650*	.56773	.049	0.0056	2.7245
		EA-95	0.5952	.58916	.573	-0.8155	2.0060
	RFD	Gly-20	-1.3650*	.56773	.049	-2.7245	-0.0056
		EA-95	-0.7698	.60984	.421	-2.2301	0.6905
	EA-95	Gly-20	-0.5952	.58916	.573	-2.0060	0.8155
		RFD	0.7698	.60984	.421	-0.6905	2.2301

Based on observed means

The error term is Mean Square (Error)= 4.165

*. The mean difference is significant at the .05 level

The post hoc analysis (Tukey-Kramer test) showed that there was a difference between the GLY-20 and RFD groups (p=0.049).

Table 4: Multiple Comparisons by Post-Hoc analysis (Tukey-Kramer Test) between COMI-back over 6 months.

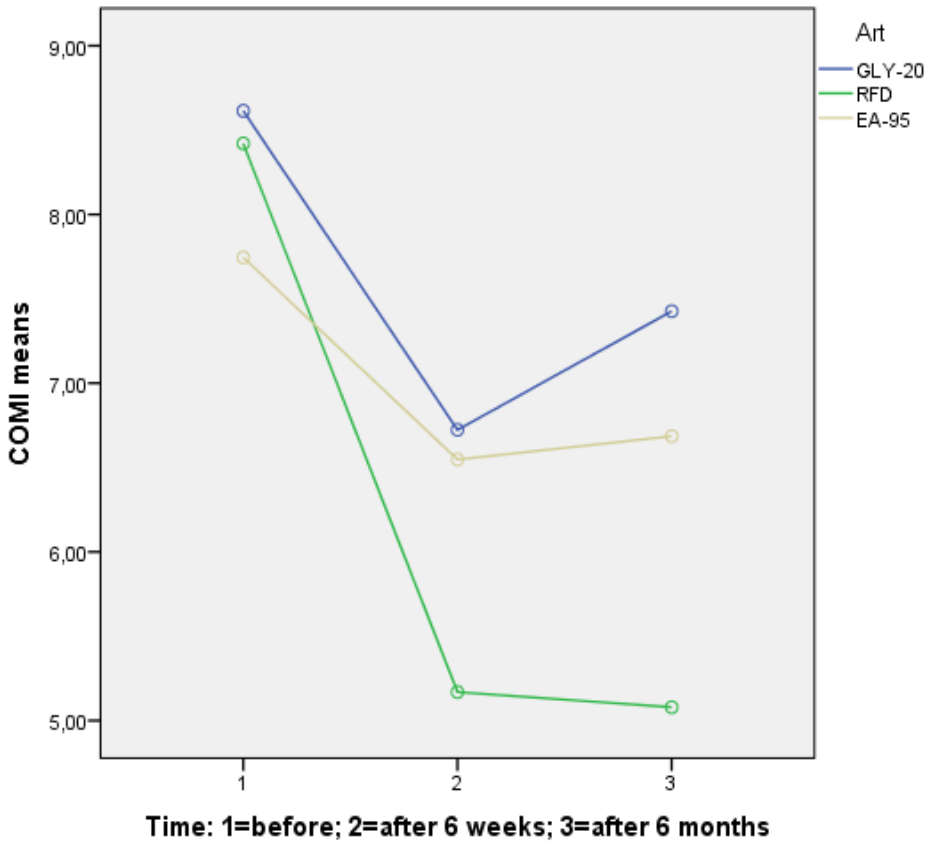

Figure 21: Estimated marginal of total means of COMI-back of the different treatment groups over 6 months

5.3 Medium-term outcome parameters

5.3.1. VAS outcomes over 12 months

A repeated measurement analysis of variance (rmANOVA) was conducted to investigate potential differences among the three treatment groups (Gly-20, RFD, and EA-95). The dependent variables were the VAS scores recorded over a period of 12 months. Assumptions of normality, homogeneity of variance-covariance matrices [the Box's M test of 0.789 indicates homogeneity of covariance matrices between groups (p=0.066)], linearity and multicolinearity were satisfied. The effect of treatment over 12 months on the VAS is significant [F=32.17; df=3/135; P<0.001]. Figure ***14***22 illustrates the total estimated marginal means of VAS over 12 months

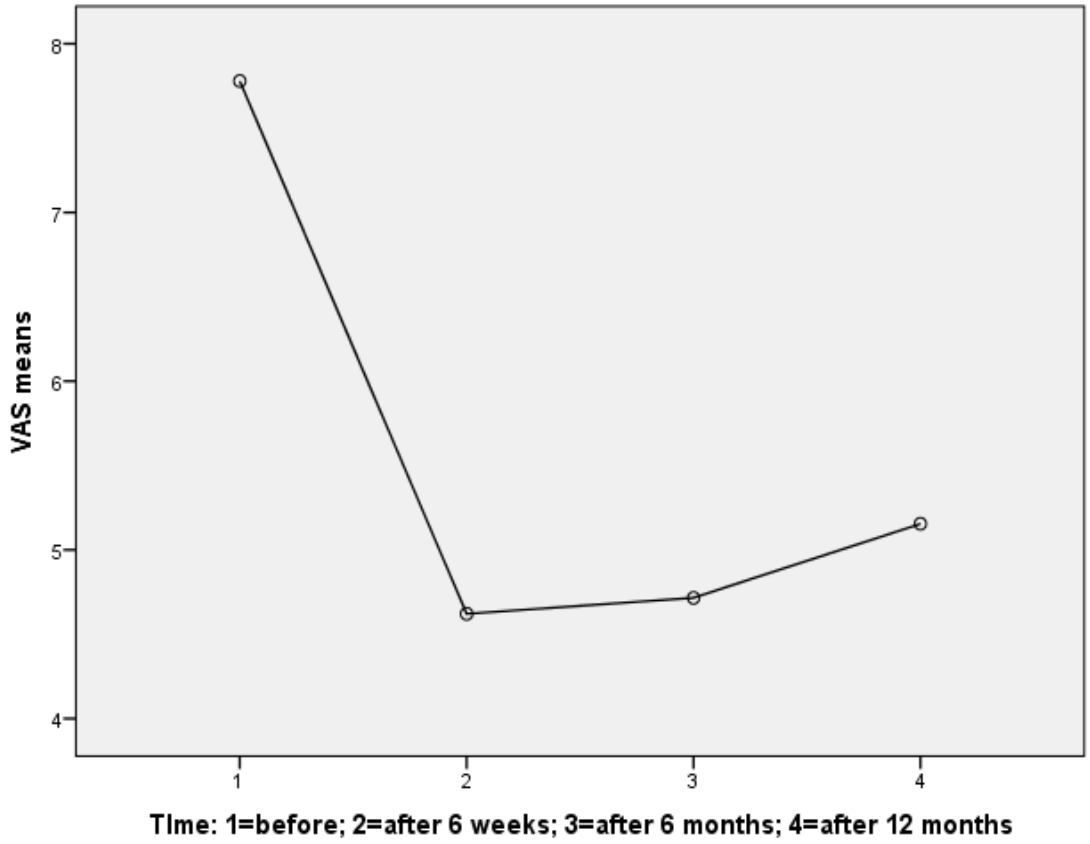

Figure 22: The total estimated marginal means of VAS over 12 months

An interaction effect time by group is also significant [F=2.69; df=6/135; p=0.017]. Tests of between-subjects effects show that the independent variables (Gly-20, RFD and EA-95) have no significant effect on the dependent variable (VAS over 12 months) [F=3.185; df=2/45; p=0.051]. Figure 23 shows the estimated marginal means of VAS of the different treatment groups over 12 months, as generated by the SPSS program.

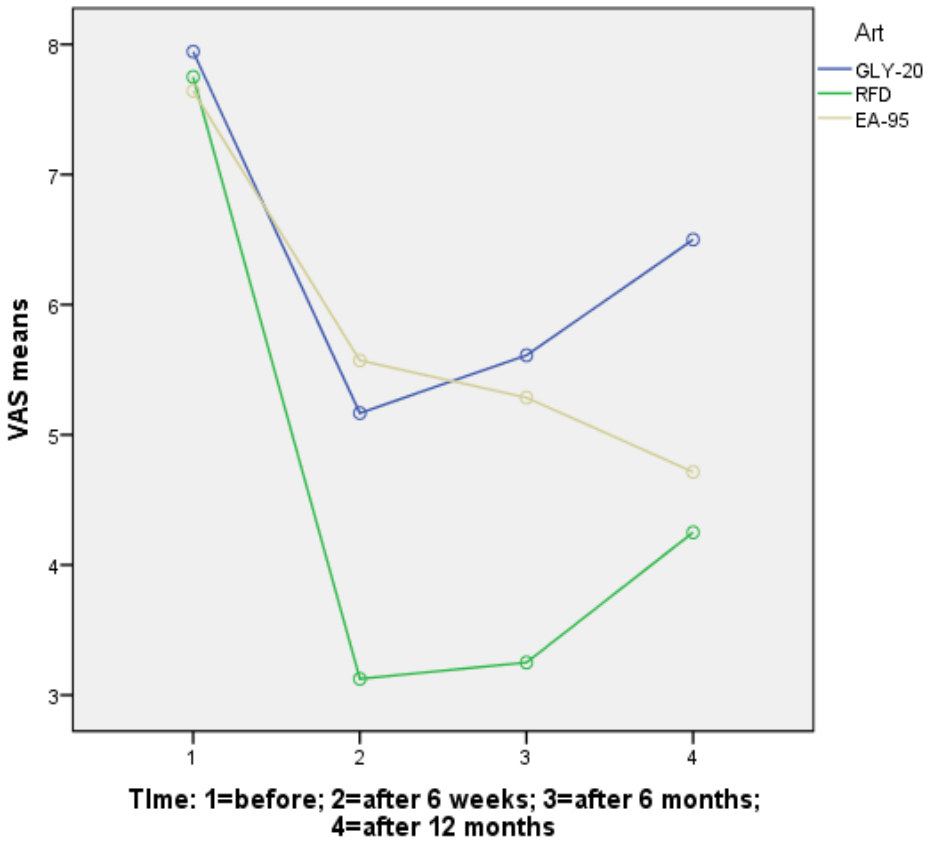

Figure 23 : The estimated marginal means of VAS of the different treatment groups over 12 months

5.3.2. COMI-back outcomes over 12 months

A repeated Measurement analysis of variance (rmANOVA) was performed to determine whether there was any difference between the 3 different management groups (Gly-20, RFD and EA-95). Dependent variables were the COMI-back over 12 months. Assumptions of normality, homogeneity of variance-covariance matrices [the Box's M test of 0.709 indicates homogeneity of covariance matrices between groups (p=0.012)], for this reason Greenhouse-Geisser correction was calculated. The effect of treatment over 12 months on the COMI-back is significant [F=20.06; df=2.54/115.8; p<0.001Greenhouse-Geisser correction]. Figure 24 illustrates the total estimated marginal means of COMI-back over 12 months.

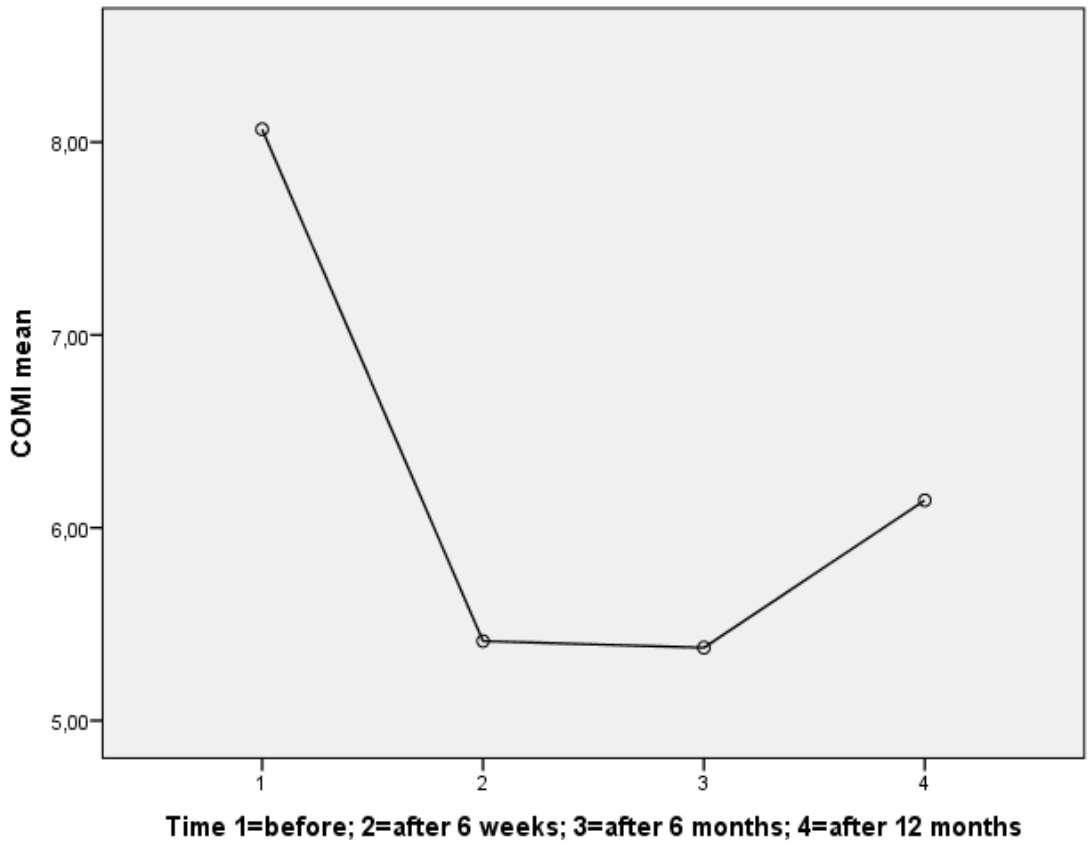

Figure 24: The total estimated marginal means of COMI-back over 12 months

An interaction effect time by group is also significant [F=2.71; df=5.07/115.8; p=0.023 Greenhouse-Geisser correction]. Tests of between-subjects effects show that the independent variables (Gly-20, RFD and EA-95) have no significant effect on the dependent variable (COMI-back over 12 months) [F=1.771; df=2/44; p=0.180]. Figure 25 illustrates the estimated marginal means of COMI-back of the different treatment groups over 12 months using the graphs generated by the SPSS program.

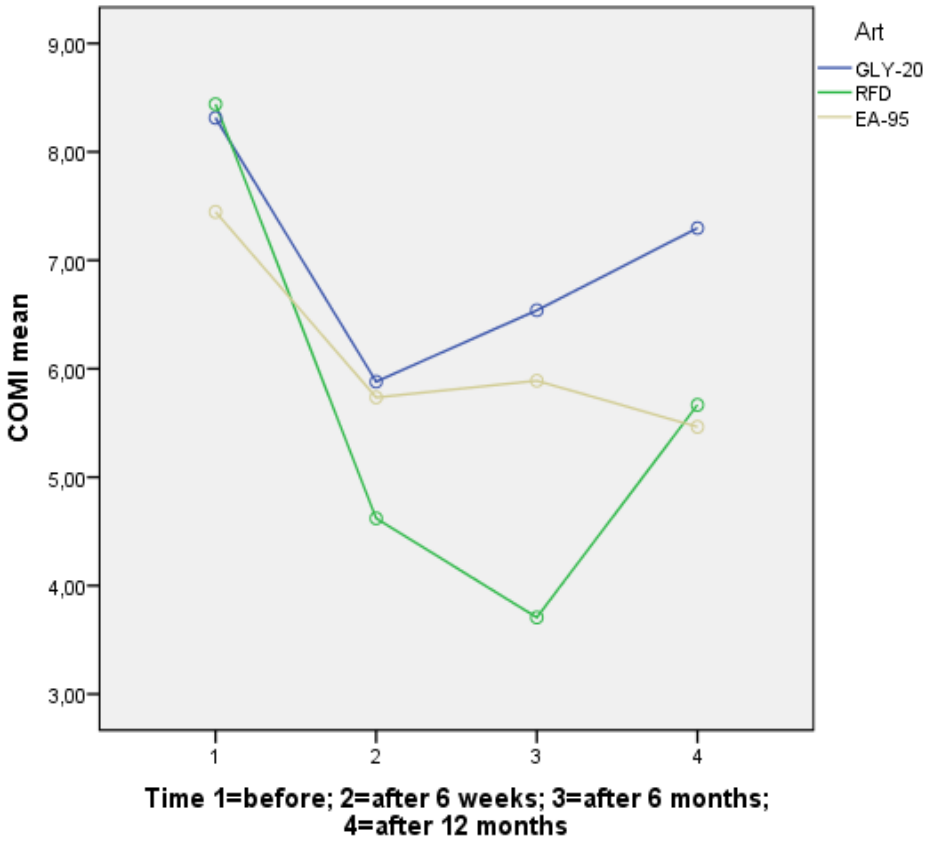

Figure 25: The estimated marginal means of COMI-back of the different treatment groups over 12 months

5.4 Descriptive Statistics over the study period

After 6 months of observation, the mean VAS and COMI-back were lower in all three intervention groups, with an overall post-intervention VAS of 5.27±3.06 and COMI-back of 6.44±3.08. Furthermore, the VAS and COMI-back were lower in the patients who received RFD than in those patients who received glycerol 20% or ethyl alcohol 95% injection therapy. After 12 months of observation, the mean VAS and COMI-back of all patients increased compared to earlier time points. However, the mean VAS and COMI-back scores did not return to baseline values, with an overall VAS of 5.23 ± 3.01 and COMI-back of 6.60± 3.13. In addition, the VAS and COMI-back were lowest in patients treated with RFD compared to the other two treatment groups, glycerol 20% and ethyl alcohol 95%, but statistical significance was not established. Descriptive statistics (mean and standard deviation of VAS and COMI-back in each study group) over the study period are summarised in Tables 5 and 6.

Figures 20 and 21 display the differences in mean of COMI-back and VAS scores between the study conditions over time.

dependent Variable		Mean	Std. Deviatian	N
VAS (Pre-Interventional)	Gly-20	8.14	1.26	35
	RFD	8.00	1.46	30
	EA-95	7.87	2.01	30
	Total	8.01	1.58	95
VAS after 6 Weeks	Gly-20	6.00	2.98	28
	RFD	3.79	2.57	24
	EA-95	6.00	3.18	21
	Total	5.27	3.06	73
VAS after 6 months	Gly-20	6.00	2.98	28
	RFD	3.79	2.57	24
	EA-95	6.00	3.18	21
	Total	5.27	3.06	73
VAS after 12 months	Gly-20	6.50	2.20	18
	RFD	4.25	3.13	16
	EA-95	4.71	3.36	14
	Total	5.23	3.01	48

Table 5: Descriptive statistics: mean and standard deviation of VAS in each study group over the study period.

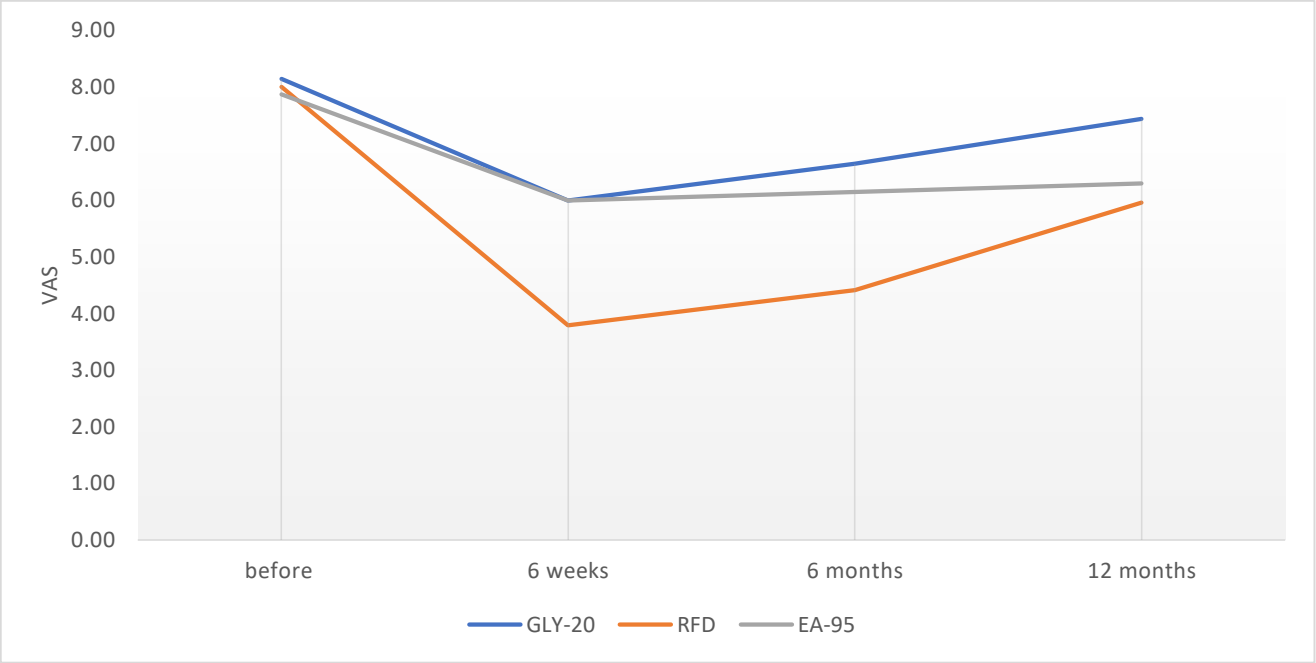

Figure 26: Differences in mean VAS scores between study conditions over time

Dependentvariable		Mean	Std. Deviatian	N
COMI-back (Pre-Interventional)	Gly-20	8.45	1.46	35
	RFD	8.45	0.94	30
	EA-95	8.02	1.55	30
	Total	8.31	1.35	95
COMI-back after 6 weeks	Gly-20	6.72	2.95	28
	RFD	5.17	2.89	24
	EA-95	6.55	3.40	21
	Total	6.16	3.10	73
COMI-back after 6 months	Gly-20	7.43	2.26	28
	RFD	5.08	3.45	24
	EA-95	6.69	3.14	21
	Total	6.44	3.08	73
COMI-back after 12 months	Gly-20	7.44	2.40	18
	RFD	5.96	3.25	16
	EA-95	6.30	3.63	14
	Total	6.60	3.13	48

Table 6: Descriptive statistics: mean and standard deviation of COMI-back in each study group over the study period

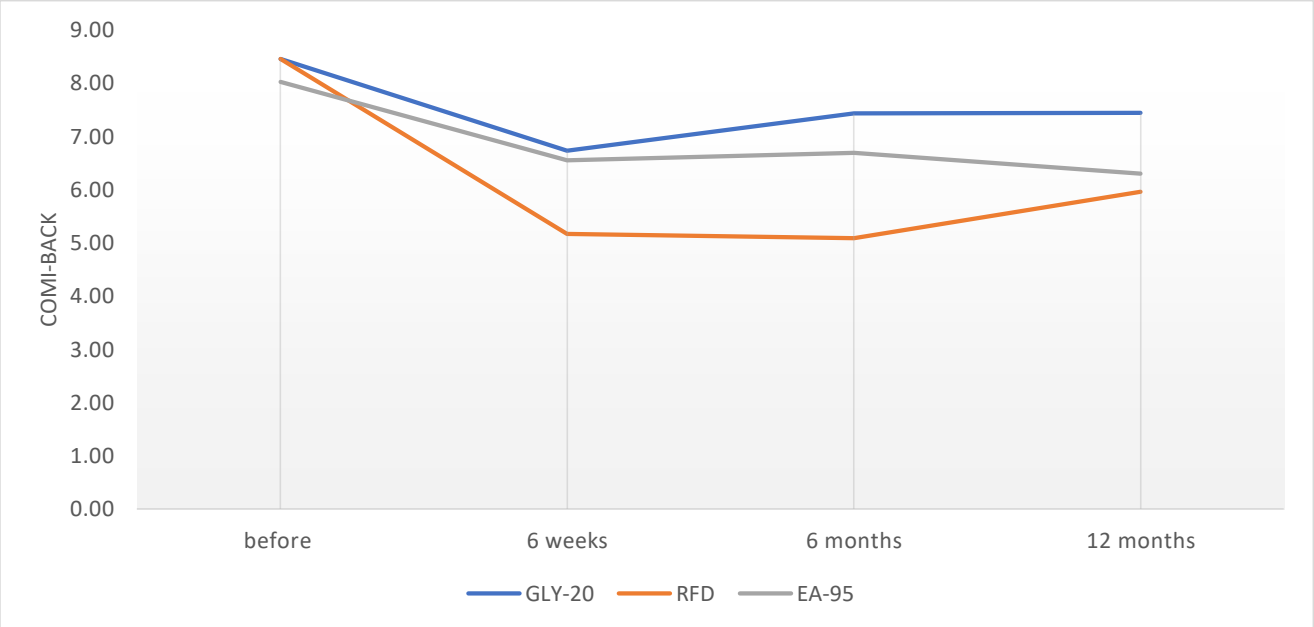

Figure 27 : Differences in mean COMI-back scores between study conditions over time

5.5 Complications

No major complications such as acute cauda equina syndrome, postinterventional bleeding, postinterventional infections or permanent motoric weakness were seen in the current study. All the documented complications in this study were reversible. Most of the complications were due to acute progression of pain symptoms upon intervention, requiring adaptation of analgesia.

Complications occurred most frequently in patients treated with ethyl alcohol 95% injection (30% complication rate in the EA-95 Group), compared with 6.67% of patients in the RFD Group and 2.9% of the patients in the Gly-20 Group reported complicated courses (Chi^2=12.54; df=2; p=0.002). Finally, according to internal clinic guidelines and due to suboptimal pain relief, eight patients were referred to multimodal pain therapy (including psychological therapy) and eleven patients underwent endoscopic rhizotomy under general anaesthesia. All complications are shown in Table 7.

	Group Gly-20	***Group RFD***	***Group EA-95***
Acute progression of pain	2,9% (1/35)	0 %	23,33% (7/30)
Reversible motor weakness	0 %	3.3% (1/30)	3.3% (1/30)
Radiculopathy and dysesthesia	0 %	3.3% (1/30)	6.67% (2/30)
Complication-rate	**2.9% (1/35)**	**6.67% (2/30)**	**30% (10/30)**
Emergency Re-hospitalization (within 48 hours after intervention)	2.9% (1/35)	0 % (0/30)	23.33% (7/30)
Repeated infiltration (after 6 months)	48.57% (17/35)	40% (12/30)	53.33% (16/30)
Endoscopic neurotomy (after 6 months)	14.29% (5/35)	1% (3/30)	1% (3/30)
Selected for multimodal pain management	2.9% (1/35)	1% (3/30)	13.33% (4/30)

Table 7: Complications in all study groups

6. Discussion

The key results of this prospective follow-up study on chronic low back pain therapy are summarized as follows:

1. Prior to intervention, patients experience more pain compared to subsequent time points after treatment as patients report higher COMI-back scores pre-interventionally than at later time points. The main effect of time was consistently statistically significant.
2. In patients with non-invasive therapy-resistant chronic low back pain due to lumbar facet arthropathy, RFD therapy is associated with improved pain relief and higher quality of life compared with therapies of EA-95 or Gly-20 injections.
3. The use of chemical neurolysis with EA-95 was associated with an increased occurrence of complications compared with treatment with RFD therapy or Gly-20 injections.

In patients without cardiac implantable electronic devices, RFD, rather than chemical neurolysis, should be considered the treatment of choice for chronic low back pain. However, if chemical neurolysis is indicated, the findings of the current study imply that Gly-20 injections should be the preferred treatment option. Given the large number of documented complications in patients treated with EA-95, it is tempting to speculate that this treatment option should be avoided in patients with CLBP.

The current study focused on both RFD and chemical alternatives. RFD therapy aims to dampen nervous system-related noxious transmission, and it is considered an established, minimally invasive treatment method for chronic low back pain. Its effectiveness has been demonstrated in clinical trials [256,264,308-311].

Radio frequency denervation (RFD) entails a current-generating source that transfers electric energy to an insulated electrode that touches the tissue. The average generated temperature by applying the electric-energy-driven probe to the tissue varies between 60°C and 80°C. The lesion size depends on the size and diameter of the needle tip, along with the temperature generated. The exposure time does not alter the tissue lesion size. Temperature-controlled radiofrequency is the preferred mode of action because it produces more standardized lesion sizes in comparison with voltage- controlled settings. This is mainly due to the defined effective range, which is determined by the size of the electrode probe. The potential risks of this treatment are primarily related to the action of needle insertion: local bleeding, local infection, and collateral damage to local structures. More specific to radiofrequency, there have been reports of sensations of transient burning pain or numbness and muscle weakness. Skin burns are a risk if the equipment is misused or damaged [319]. Post-denervation neuritis has also been reported in the literature and is described as a

sunburn-like feeling that usually resolves weeks after the procedure [320]. Overall, the complication rates of RFD are generally low, ranging from 1% to 6.5%. No long-term complications were identified in the literature review conducted for this study [162].

In addition to radio frequency denervation, the current study focused on a comparison with chemical neurolysis, which is accepted in the field of oncological pain management [321]. The benefits of chemical neurolysis are considered to largely outweigh its risks. However, according to current guidelines from the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine, chemical neurolysis should not be routinely used for the treatment of non-oncological chronic pain [34,320]. Nevertheless, chemical neurolysis is a technique that requires extreme attention to detail, both anatomically and physiologically. It relies on the use of advanced imaging techniques for the successful placement of chemicals (primarily alcohol or phenol) in close proximity to the targeted neural structures thought to be responsible for nociception. The relatively inexpensive and reliable chemical agents and related surgical techniques keep them attractive in today's interventional pain management practice.

Chemical neurolysis is most often performed with phenol, ethyl alcohol, or, less commonly, glycerol [295]. Hypertonic saline, ammonium salt solutions, and chlorocresol have also been used in the past [322,323]. In short, these agents are believed to disrupt the transmission of pain signals. More specifically, phenol diffuses into the axon, where it causes Wallerian degeneration of the proteins. The effects of phenol consist of a combination of neurotoxicity and ischemia. Histological analyses have demonstrated nonselective nerve destruction, muscle atrophy, and necrosis after undergoing phenol injections. An additional benefit of neurolysis with phenol is its local anesthetic effect. This leads to additional pain relief and better tolerance. Local anesthesia is achieved at concentrations below 1%, without neurolysis. To achieve maximum neurolysis, it is theoretically needed to inject 12% phenol, which is the maximum solubility of phenol in aqueous solution. At concentrations above 6%, neural side effects are predictable, including the risk of development of adhesive arachnoiditis, meningitis and spinal cord infarction, which increases if the chemical is applied intrathecally. The most worrisome toxicities that occur after intravascular injection include cardiovascular collapse and central nervous system depression. Furthermore, other organ systems can also be affected, such as the development of chronic intoxication and hepatic toxicity, which can lead to gastrointestinal and renal toxicity as well as skin rashes [157,295,321].

In contrast, alcohol produces a nonselective destruction of nervous system tissue by destruction of the lipid bilayer and denaturing cell membrane proteins. In that way, phospholipids, cerebrosides, and cholesterol are extracted from neuronal cell membranes, which then collapse and induce cell necrosis. Moreover, mucoproteins are denatured and sclerosis of the nerve fibers and the myelin sheath itself occurs. The primary type of damage

is the mechanism of Wallerian degeneration. Alcohol spares the Schwann cell tubes, so there is a possibility of neuron regeneration, with the exception of: the spinal ganglion [22,295,296,321]. Alcohol neurolysis evokes an initial burning sensation along the nerve root, which is followed by numbness along the same distribution pattern. As ethyl alcohol lacks the local anaesthetic properties of phenol injection fluids, it is usually more painful to inject. However, the intensity and duration of nerve blocking are less pronounced with phenol than with ethyl-alcohol [295]. Phenol injections are not performed in our institution due to the high risk of severe side effects when entering the circulation; we prefer to use 20% Glycerol solutions, which carry a low risk in case of systemic spreading. Glycerol is a highly viscous and neurolytic agent. It is an established blocking agent acting at the Gasserian ganglion by its hyperosmolar action, and is frequently used to treat trigeminal pain [324]. However, previous studies have suggested that its analgesic effects are temporary and reversible, or the use of glycerol appears to be limited to blocking the Gasserian ganglion, but is effective [321,325]. The concentration of Glycerol used for injections at our institution is based on experiences from other fields. Although no specific titration studies have been performed by the authors. Moreover, there is no literature on comparative clinical studies focusing on this topic.

Chemical neurolysis has some relevant disadvantages. Possible complications include cardiac arrhythmias, hypotension, necrosis of the skin and non-target tissue, and central nervous system excitation. Furthermore, in the specific case of ethyl alcohol neurolysis, post-neurolytic chemical neuritis with severe burning pain in the distribution area of the nerve has been documented. Unfortunately, the incidence of post-neurolytic chemical neuritis is high and rates of up to 10 % have been reported. It has been assumed that this complication is due to the incomplete destruction of somatic nerves and the subsequent painful regeneration of these nerves [320,321,326]. The results of the current study highlight the importance of this issue, as a significant proportion of patients treated with ethyl alcohol suffered from severe pain development, which in some cases even required emergency hospital admission.

Another potential risk of chemical neurolysis is uncontrolled spread of the injection material. Unintentional diffusion of fluids from the paravertebral groove into adjacent areas, including the neuroforamina, epidural space and even cerebrospinal fluid (CSF), can be harmful and is difficult to control. Cases of persistent paraplegia associated with chemical neurolysis have been documented [327]. In the present study, complications of motor paralysis or paraplegia associated with the different types of chemical neurolysis did not occur; however, several patients experienced transient dysesthesia and hyperesthesia after the procedure. Furthermore, no infectious complications or post-operative bleeding/hematoma formations occurred. This underlines the safety of the investigated interventions when performed by experiences physicians that have a profound knowledge of the local anatomy and imaging techniques (such as qualified spine surgeons). Additionally, increased pain upon intervention

was found more frequently in the ethanol-group. This may be due to local spread of the fluid. In order to minimise the incidence of this adverse event, it may be advisable to consider modifying the dosage and concentration, or incorporating additional contrast-enhanced imaging before injection. Nevertheless, as the alternative treatment options were not associated with increased temporary post-interventional pain, we prefer to proceed with other techniques than ethanol-infiltrations.

With regard to the side effects, it can be summarized that the severity and frequency of side effects of the EA-95 intervention compared to the RFD and Gly-20 intervention argue for the limited use of neurolysis with EA-95, e.g. when RFD and Gly-20 are contraindicated. In addition, the low severity and comparatively low frequency of side effects of precise application of the RFD and Gly-20 method argue for their use as the standard method for indicated minimally invasive intervention in chronic low back pain.

According to our protocols, in the usual case of a strong pain reduction after the procedure, we decided to reduce the pain medication directly before the procedure. Post-procedural escalation of pain medication was not routinely performed. It is reasonable to assume that to overcome transient pain escalation in individuals selected for chemical neurolysis, these patients would benefit from parallel routine, transiently increased oral pain medication.

In our comparative study, radiofrequency denervation was associated with an overall more favorable outcome than EA-95. This is in contrast to a cohort study by Joo et al. [152]. Their main finding is that alcohol ablation resulted in prolonged pain relief and improved quality of life compared to repeated radiofrequency denervation therapy in patients with recurrent thoracolumbar facet joint pain during a 24-month observation period. The discrepancy between their results and our data is most likely due to differences in patient inclusion criteria. More than 50% of the patients in the study conducted by Joo et al. had undergone either previous radiofrequency therapy or spinal surgery, or had been diagnosed with severe kyphoscoliosis. Their patient cohort was very heterogeneous, which the authors stated as one of the main shortcomings of their study. Consequently, their cohort differed considerably from the patients in our study, as all previously mentioned interventions and diagnoses are absolute contraindications [152].

Nevertheless, it is reasonable to hypothesize that chemical neurolysis with ethyl alcohol is preferable in patients with severe concurrent spinal diagnoses and/or previous surgical procedures, while radiofrequency denervation is more beneficial in patients with isolated chronic low back pain. Unfortunately, Joo et al. used a binary outcome scale to determine pain relief, so it is not possible to compare the overall efficacy of the treatments used in the two studies [152]. The overall effectiveness of RFD documented in that study four weeks after surgery ranged from 42% to 93%. Long-term effectiveness, defined as at least 12 months with pain relief of 50% or more, also ranged from 47% to 87% [253,308,310].

These results are consistent with our observations here; after RFD, the VAS decreased significantly from 8.00±1.46 to 3.79±2.57 and 4.25±3.13 at 6 weeks and 12 months, respectively.

The VAS scores were not worse than baseline at any of the time points measured (6 weeks, 6 months, and 12 months). This reflects the significantly worse outcomes of EA-95 therapy in this particular subgroup. As previously described, the cohort treated with EA-95 chemical neurolysis had significantly worse outcomes in terms of pain medication requirements and VAS scores compared to the RFD and Gly-20 condition groups.

Unfortunately, not all treatment groups are significantly different from each other at all time points studied. This can be explained by several factors, the most obvious of which is the relationship between statistical power, the heterogeneity of the biological/medical parameters of the patients in the group (biological noise), and the size of the cohort. In follow-up studies, the number of patients per group should be increased if other patient characteristics besides treatment are very heterogeneous. In addition, the patient characteristics with the highest dispersion should be recorded and included in the statistical evaluation. Nevertheless, the clear difference in outcomes in this study at the short-term time points is a clear decisive argument for opting for this intervention, as it has a positive impact on patients' quality of life, even if only in the short term, and it would contribute to patients taking concomitant measures during this time, such as reconstructive measures to strengthen the back muscles and psychological and behavioral support.

A major problem in pain-treatment studies is the influence of confounding non-treatment factors. In this context, confounding is often referred to as "mixing of effects"[328], where the effects of the studied intervention on a particular result are variegated with the effects of additional (set of) factors. This often results in a misrepresentation and misinterpretation of the relationship between factors. In a clinical trial, this situation may arise if there is a difference in the distribution of a known or unknown prognostic factor between the compared groups. To address this issue in further studies all potential confounders should be measured and reported. Patient characteristics (not only in spine care studies) are often incorrectly recorded or not in sufficient detail for the study to be able to claim significant statements. Basically, patient biological and (patho-)physiological parameters are very important and valuable to quantify and to report as they can be potential confounders. Diagnostic characteristics, comorbidities and any factors that could affect patient outcomes must also be part of the study design for each study group. All of these characteristics, attributes and factors can potentially influence the connection between the 'exposure' of interest (e.g. pharmacological or surgical treatment) and the outcome of the intervention (e.g. patient function, quality of life). The design and measurement of these qualities goes a long way towards sorting the “mixing of effects out” by addressing the role of confounding factors [329].

Additional options to deal with the large number of potential confounders are to design novel prospective studies in very specific and well defined-patient groups. Additional multivariable analysis may result in better identification of essential factors that affect outcome in similar patient cohorts as investigated in the current study. The use of novel, well validated questionnaires for patients with spinal pain may also result in better standardization of groups and interpretation of subsequent findings of therapeutic studies in the field of spinal pain.

Statistically significant findings in the current study may partly be absent due to the small sample size of the current study. Some trends that have been identified should be investigated in later studies on larger cohorts. The temporary significant findings may be the result of recurrence of complaints due to the limited duration of the pain-interventions. Furthermore, other physical and psychological factors may play a role. However, for now, this is all speculation as this was beyond the scope of the current project. Future investigations, such as questionnaire studies on this cohort may gain more insights into the key factors that explain the fading out of the initial effects of the investigated interventions.

The current prospective study has further limitations. It provides data from only one year of follow-up. However, because we defined strict inclusion and exclusion criteria, we were able to assemble a homogeneous cohort of patients. In addition, the number of missing parameters is minimal due to careful data collection. No randomization was performed, but comparable study groups were formed because patients had different treatment preferences. Consequently, the baseline parameter criteria did not show significant differences in terms of final outcomes.

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Zusammenfassung in deutscher Sprache

Chronische Rückenschmerzen gelten weltweit als eines der größten Gesundheitsprobleme [1,2]. Nichttraumatische Kreuzschmerzen sind mit einer hohen Rate an Behinderungen und Arbeitsunfähigkeit verbunden [3-5]. Die Pathophysiologie chronischer Kreuzschmerzen ist multifaktoriell. Dabei sind die lumbalen Facettengelenke (zygapophysial) eine allgemein anerkannte Ursache für chronische Rückenschmerzen [6-8].

Zur Behandlung wiederkehrender Schmerzen bei lumbaler Facettenarthropathie haben sich verschiedene minimalinvasive Behandlungsmethoden etabliert. Dazu gehören die Radiofrequenz-Desenervation (RFD) sowie die chemische Neurolyse durch Injektion von Ethylalkohol (50 % - 100 %), Phenol (5 % - 10 %) oder Glycerin (20 % - 100 %) [15-26].

In dieser Studie wurden die Auswirkungen der RFD und der chemischen Neurolyse mit Ethylalkohol 95 % und Glycerin 20 % verglichen. Außerdem wurden die kurz- und mittelfristigen klinischen Ergebnisse dieser verschiedenen Behandlungsmethoden ermittelt. Dazu wurde eine prospektive Kohortenstudie bei erwachsenen Patienten mit rezidivierenden chronischen Rückenschmerzen bei lumbaler Facettenarthropathie durchgeführt, die auf nichtinvasive Therapien und Steroidinjektionen nicht angesprochen hatten. Zur Erfassung des Schmerzempfindens wurde die Visuelle Analogskala (VAS) und zur Messung der Ergebnisparameter zu verschiedenen Zeitpunkten der Studie der Core Outcome Measures Index für den Rücken (COMI-back) eingesetzt.

Die Studie zeigt, dass bei Patienten mit wiederkehrenden Kreuzschmerzen aufgrund einer lumbalen Facettenarthropathie die RFD-Therapie im Vergleich zur chemischen Neurolyse mit einer besseren Schmerzlinderung und Lebensqualität verbunden ist. Darüber hinaus wurden bei Patienten, die eine Neurolyse mit 95 % Ethylalkohol erhielten, mehr Komplikationen beobachtet als bei Patienten, die eine RFD-Therapie oder eine Neurolyse mit 20 % Glycerin erhielten. Sofern keine Kontraindikationen, wie z. B. Herzschrittmacher oder Cochlea-Implantate vorliegen, wird nach den Ergebnissen der Studie bei Patienten mit chronischen Kreuzschmerzen, die auf eine konservative Therapie nicht ansprechen, die RFD-Therapie empfohlen. Wenn die RFD-Therapie kontraindiziert ist, wird die chemische Neurolyse mit 20 % Glycerin empfohlen. Weitere Untersuchungen einschließlich randomisierter Studien sind erforderlich, um spezifische Patientengruppen zu identifizieren, die am meisten von semi-invasiven Eingriffen bei rezidivierenden chronischen Rückenschmerzen lumbaler Facettenarthropathie profitieren und auf nicht-invasive Therapien nicht ansprechen.

Vorabveröffentlichungen von Ergebnissen

Teile der vorgelegten Arbeit wurden auf 2 Kongressen (**15. Deutscher Wirbelsäulenkongress (DWG)- 2020** und **73. Jahrestagung der Deutschen Gesellschaft für Neurochirurgie - 2021**) angenommen und vorgetragen sowie Das Abstrakt wurde bei der internationalen Zeitschrift „**European Spine Journal (2020) 29:2853–2939, Seite 2873-V44**“ angenommen und veröffentlicht.

Auflistung der eigenen Publikationen

Afifi A., Ringe M., Sobottke R., Oikonomidis S., Teuben M.Das Paper (**Lumbar Facet Joint Radiofrequency Denervation Therapy for Chronic Low Back Pain: Enhanced Outcome Compared with Chemical Neurolysis (Ethyl Alcohol 95% or Glycerol 20%))**wurde**am 09. Juli 2021** bei der Zeitschrift „**International Journal of SpineSurgery**(Ref.:Ms. No. IJSSURGERY-D-21-00146R1)“ angenommen und im Februar 2022 veröffentlicht. Int J SpineSurg. 2022 Feb;16(1):33-41. doi: 10.14444/8175. Epub 2022 Feb 17.
PMID: 35177532; PMCID: PMC9519069.

Schriftliche Erklärung und Bestätigung der Ko-Autoren

Bei der Auswahl und Auswertung des Materials sowie bei der Korrektur des Manuskriptes wurde Unterstützungsleistungen von der Ko-Autoren erhalten. Die unterschreibende schriftliche Erklärung und Bestätigung der Ko-Autoren sind angehängt (Anhang II)

Anhang

I. Anhang I: COMI Back Formulae
II. Anhang II: schriftliche Erklärung und Bestätigung der Ko-Autoren
III. Anhang III: Erklärung zu statistischer Beratung

Anhang I

DWG Patient Core Outcome Measures Index (COMI) Rücken konservativ

Deutsche Wirbelsäulengesellschaft: Wirbelsäulenregister

Patienteninformationen

Kernfragen

KERNFRAGEN

Erfassungsdatum (tt.mm.jjjj) ☐☐☐

Untersuchungsintervall

- ○ vor Behandlung
- ○ 6 Wochen
- ○ 6 Monate
- ○ 1 Jahr
- ○ 3 Jahre
- ○ 5 Jahre
- ○ bei Entlassung (Abschluss)
- ○ 3 Monate
- ○ 9 Monate
- ○ 2 Jahre
- ○ 4 Jahre
- ○ > 5 Jahre

Spezifizieren Sie Untersuchungsintervall > 5 Jahre (Monate) (61 - 240) _____

COMI-Score _____

RÜCKENBESCHWERDEN können Rückenschmerzen und/oder Schmerzen im Gesäss, Bein oder Fuss sowie zu Kribbeln, Taubheit oder anderen Missempfindungen im Rücken, Gesäss, Bein oder Fuss führen.

1. Welche Beschwerden belasten Sie AM STÄRKSTEN?

- ○ Schmerzen im Rücken
- ○ Kribbeln, Taubheit oder andere Missempfindungen im Rücken/Bein/Gesäss
- ○ Schmerzen im Bein/Gesäss
- ○ keine der aufgeführten Beschwerden

Für die folgenden 2 Fragen (2a und 2b) bitten wir Sie die Intensität Ihrer Schmerzen auf einer Skala zwischen 0 und 10 anzugeben, wobei 0=KEINE Schmerzen und 10=STÄRKSTE vorstellbare Schmerzen bedeutet. Wir bitten Sie, zwischen RÜCKEN- und BEINSCHMERZEN zu unterscheiden.

2.a Wie stark waren Ihre RÜCKENSCHMERZEN in der letzen Woche? (0 - 10) _____

2.b Wie stark waren Ihre BEIN-/GESÄSSSCHMERZEN in der letzen Woche? (0 - 10) _____

Rückenbezogene Funktion

3. Wie stark haben Ihre Rückenbeschwerden Ihre NORMALEN AUFGABEN (Arbeit und zu Hause) IN DER
LETZTEN WOCHE BEEINTRÄCHTIGT?

- ◯ gar nicht
- ◯ ein wenig
- ◯ mässig
- ◯ erheblich
- ◯ sehr stark

Wohlbefinden

4. Wie würden Sie sich fühlen, wenn Sie den REST IHRES LEBENS MIT IHREN DERZEITIGEN Rücken-
beschwerden leben müssten?

- ◯ sehr zufrieden
- ◯ etwas zufrieden
- ◯ weder zufrieden noch unzufrieden
- ◯ etwas unzufrieden
- ◯ sehr unzufrieden

5. Bitte blicken Sie AUF DIE LETZTE WOCHE zurück. Wie würden Sie Ihre Lebensqualität beurteilen?

- ◯ sehr gut
- ◯ gut
- ◯ mittelmässig
- ◯ schlecht
- ◯ sehr schlecht

Körperliche Einschränkungen

6. An wievielen Tagen IN DEN LETZTEN 4 WOCHEN haben Ihre Rückenbeschwerden
Sie gezwungen,
Ihre GEWOHNTEN TÄTIGKEITEN (Arbeit, Hausarbeit, Schule, Freizeitaktivitäten) EINZUSCHRÄNKEN?

- ◯ 0 Tage
- ◯ zwischen 1 und 7 Tagen
- ◯ zwischen 8 und 14 Tagen
- ◯ zwischen 15 und 21 Tagen
- ◯ an mehr als 21 Tagen

Soziale Einschränkungen

7. An wievielen Tagen IN DEN LETZTEN 4 WOCHEN haben Ihre Rückenbeschwerden
Sie DARAN GEHINDERT,
zur ARBEIT zu gehen (Arbeit, Schule, Hausarbeit)?

- ◯ 0 Tage
- ◯ zwischen 1 und 7 Tagen
- ◯ zwischen 8 und 14 Tagen
- ◯ zwischen 15 und 21 Tagen
- ◯ an mehr als 21 Tagen

Beantworten Sie die folgenden Fragen nur wenn Sie den Fragebogen NACH der Operation ausfüllen

Komplikationen/weitere Operationen

8a. Sind ALS FOLGE DER OPERATION IN UNSEREM HOSPITAL KOMPLIKATIONEN aufgetreten
(wie z.B. Störung der Wundheilung, Lähmung, Gefühlsstörungen)?

- ◯ nein
- ◯ ja

Wenn ja, bitte beschreiben Sie diese (optional) [ ]

8b. Wie beeinträchtigend/störend waren diese Komplikationen?

- ◯ gar nicht beeinträchtigend/störend
- ◯ ein wenig beeinträchtigend/störend
- ◯ mässig beeinträchtigend/störend
- ◯ erheblich beeinträchtigend/störend
- ◯ sehr stark beeinträchigend/störend

9. Wurden Sie SEIT DER OPERATION bei uns IN EINEM ANDEREN HOSPITAL ODER ERNEUT BEI UNS an der Lendenwirbelsäule (am Rücken) operiert?

- ◯ nein
- ◯ Ja, aber an einer anderen Stelle der Lendenwirbelsäule
- ◯ Ja, an derselben Stelle der Lendenwirbelsäule (gleiches Segment)

Zufriedenheit mit der Behandlung

10. Wie zufrieden waren Sie bisher mit der BEHANDLUNG Ihrer Rückenbeschwerden IN UNSEREM HOSPITAL?

- ◯ sehr zufrieden
- ◯ etwas zufrieden
- ◯ weder zufrieden noch unzufrieden
- ◯ etwas unzufrieden
- ◯ sehr unzufrieden

Eigene Beurteilung des Ergebnisses

11. Wie hat Ihnen die BEHANDLUNG Ihrer Rückenbeschwerden (OPERATION) IN UNSEREM HOSPITAL insgesamt geholfen?

- ◯ sehr geholfen
- ◯ geholfen
- ◯ nur wenig geholfen
- ◯ nicht geholfen
- ◯ geschadet

Anhang II

Promotionsbüro
Medizinische Fakultät
Universität zu Köln

Würselen , den 21.10.2021

Sehr geehrte Damen und Herren,

hiermit bestätigen wir Ihnen, dass Herr Anas Afifi, geboren am 22.08.1986 in Göttingen, den wesentlichen Teil der Promotionsarbeit mit dem folgenden Titel geleistet hat:

„Radiofrequenzdenervierung für Facettengelenksarthropathie hat bessere Ergebnisse in der Schmerzreduktion und Lebensqualität im Vergleich zur chemischen Neurolyse (Ethylalkohol 95% oder Glycerol 20%)“

„Radiofrequency denervation therapy for lumbar facet joint arthropathy: enhanced outcome compared with chemical neurolysis (Ethyl alcohol 95% or Glycerol 20%)”

Die Annahme als Doktorand und die damit verbundene Ausgabe des Promotionsthemas erfolgte am 01.12.2017, Herr Afifi arbeitet in der Klinik für Wirbelsäulenchirurgie, Neurochirurgie und spezielle Orthopädie am Rhein Maas Klinikum in Würselen und wird dort betreut von Chefarzt Prof. Dr. med. R. Sobottke.

Teile der vorgelegten Arbeit wurden bereits auf zwei Kongressen (15. Deutscher Wirbelsäulenkongress (DWG) 2020; 73. Jahrestagung der Deutschen Gesellschaft für Neurochirurgie 2021) angenommen und vorgetragen.
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Der oben genannte wesentliche Teil der Arbeit bestand in den folgenden Tätigkeiten:

Literaturrecherche, Formulierung der Fragestellung, Datenerhebung aus den Krankenakten, Datenauswertung mit Hilfe des Statistikprogrammes SPSS, Interpretation der Daten, Niederschrift der erhobenen Ergebnisse und Anfertigung der Tabellen und Diagramme, Diskussion der erhobenen Ergebnisse und Vergleich mit Studien aus der Literatur.

Mit der Betreuung und Korrektur des Manuskriptes hat Herr Afifi Unterstützungsleistungen folgender Ko-Autoren erhalten:

Herr Prof. Dr. med. Rolf Sobottke
Herr Dr. med. Mathis Julius Ringe
Herr Michel Paul Johan Teuben
Herr Dr. med. Stavros Oikonomidis

Prof. Dr. med. Rolf Sobottke
Chefarzt
Zentrum für Orthopädie, Unfallchirurgie und
Wiederherstellungschirurgie
Klinik für Wirbelsäulenchirurgie,
Neurochirurgie und Spezielle Orthopädie
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Prof. Dr. med. R. Sobottke
Doktorvater (nach §4 Promotionsordnung)

Dr. med. Mathis Ringe
Leitender Oberarzt
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Tel.: 02405 - 62 - 8212

Dr. med. M. J. Ringe

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Medizinische Fakultät
Universität zu Köln

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Herr Michel Paul Johan Teuben
Herr Dr. med. Stavros Oikonomidis

Michel P. J. Teuben

Anhang III

Universität zu Köln

Medizinische Fakultät • Joseph-Stelzmann-Str. 20 • 50931 Köln

Köln, 19.02.2024

Erklärung zu statistischer Beratung

Hiermit erkläre ich, Anas Afifi (Name),

dass ich im Rahmen meiner Dissertation mit dem Titel:

Lumbar facet joint radiofrequency denervation therapy for recurrent chronic low back pain: enhance outcome compared with chemical neurolysis

eine statische Beratung in Anspruch genommen habe. Diese Beratung erfolgte durch:

☐ Das Institut für Medizinische Statistik und Bioinformatik der Medizinischen Fakultät der Universität zu Köln
Die Dissertation muss vor Einreichung dem ISMB vorgelegt werden, damit hier eine Prüfung der umgesetzten Statistik erfolgen kann. Sollte eine statistische Beratung erfolgt sein und dies hier nicht angegeben werden, wird das Institut für Medizinische Statistik und Bioinformatik bei Offenlegung der Dissertationen einen Einspruch einlegen müssen und das Promotionsverfahren verlängert sich auf unbestimmte Zeit.

☑ Eine externe Beratungsstelle, bitte Adresse angeben:

Marc Brügmann - Rhein Maas Klinikum
Pain Therapy and Palliative Care Diplom Psychologe
Research Assistant- RWTH Aachen 06/95 - 06/2004

Bitte geben Sie auch an in welchem Umfang die Beratung erfolgte:

Datenauswertung mit Hilfe Statistikprogrammes SPSS sowie Interpretation der Daten

Medizinische Fakultät

Der Dekan

Univ-Prof. Dr. G. R. Fink

Medizinisches Dekanat Promotionsbüro

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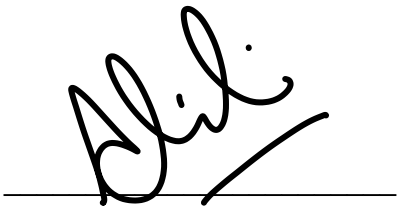
Köln, 19/2/24

☐ Es ist keine statistische Beratung erfolgt:



Unterschrift des Promovenden

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Der Dekan

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