16 TREATMENT METHODS FOR LUMBAR PAIN AND THEIR MECHANISMS OF ACTION

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Approximately 75-85% of the population will encounter lumbar pain in their lifetime. Lumbar pain is the most common pain in patients under the age of 45 and the third most common pain in patients over the age of 45. Lumbar pain threatens the quality of life and socioeconomic status of patients and can be caused by genetic, personal and environmental factors. However, it is difficult to detect the primary etiologic factor for lumbar pain [1].

Discs are the primary stabilizers of lumbar spinal segments, and their degeneration causes chronic pain and disability. Although disc degeneration increases with age, it can be seen in younger patients. Pathophysiological examinations of degenerative discs show a decrease in extracellular matrix production, which results in fissures and tears of the nucleus pulpous, degeneration in collagen fibers of the annulus fibrosus and microfractures in the endplate [2,3]. In healthy discs, one third of the outer layer of annulus fibrosus is innervated, and in degenerated discs, the plexus of nerves and veins is displaced toward the inner layers [4].

Degenerative disc disease has three phases. The first phase is the dysfunction phase, which occurs between the ages of 15-45. During this phase, annular or radial fissures in the annulus and synovitis at the facet joint can be observed. The second phase is the instability phase, which occurs between the ages of 35-70. Deformation of inner disc structures, progressive disc resorption and facet joints with laxity, subluxation and joint erosion are characteristic features of phase two. The last phase, stabilization, is observed in patients over the age of 60.

Hypertrophy in the facet joints and osteophytes in the endplates from the progression of degeneration results in consolidation of the facet joints and ankylosis [5].

Many studies and reviews have examined the efficiencies of lumbar pain treatments. The conservative treatment methods for lumbar pain include non-steroidal anti-inflammatory drugs, steroids, muscle relaxants, opioid analgesics, antidepressants, anticonvulsants, physiotherapy methods, manipulation and acupuncture.

1. Drug Treatments

Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (Paracetamol) group: The causes of pain should be addressed before discussing the mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs). The general pathophysiology of pain can be categorized into three sources: nociceptive pain (somatic, visceral), non-nociceptive pain (neuropathic, psychogenic) and unclassified pain syndromes (myofascial pain syndrome, fibromyalgia syndrome) [6].

For nociceptive pain, activation of the cyclooxygenase (COX) enzyme promotes prostaglandin (PG) release from injured and inflamed tissues, thereby increasing the sensitivity of neuronal structures. The pain is usually due to the activation of nociceptors. PG is a hormone produced by the COX-1 enzyme that exists in all tissues. The COX-2 enzyme is dominant in some tissues, such as the central nervous system, vein walls, the heart and the kidneys. Nociceptors

are stimulated by the secretion of prostaglandin endoperoxide 2 (PGE-2) by COX-2 from inflamed and traumatized tissues. In peripheral hyperalgesia, phosphorylation from cyclic adenosine monophosphate (cAMP) production from PGE-2 receptors and activation of the transient receptor potential vanilloid 1 (*TRPV1*) protein, also referred to as "capsaicin receptor," stimulates C-fibers. Central hyperalgesia is caused by PG synthesis at the anterior horn of the spinal cord, due to COX-2 activation. Increased PGE-2 production at the anterior horn of the spinal cord decreases the number of open chloride channels, which are also glycine receptors. A decrease in chloride passage into the second neuron also decreases hyperpolarization. Peripheral and central inhibition of PG production constitutes the principal mechanism of action of COX inhibitors (NSAIDs) [7,8].

Acetaminophen is an analgesic and antipyretic drug with a mechanism of action that is not clearly understood. PG is, conversely, accepted as a weak inhibitor of PG synthesis. From *in vivo* studies, PG acts as a COX-2 inhibitor; however, the drug's anti-inflammatory effect is weak. In recent years, COX-3 has been discovered in the brain and the spinal cord, and it is thought that acetaminophen has analgesic and antipyretic effects over the central nervous system through specifically inhibiting COX-3. In addition, acetaminophen also exhibits analgesic effects through modulating the endogenous vanilloid system; acetaminophen inhibits the uptake of vanilloid by neurons and prevents activation of TRPV1 receptors [9-12].

There are numerous studies evaluating the efficacy of non-steroidal anti-inflammatory drugs in the treatment of lumbar pain, comparing their effects to other analgesics and placebo. A Cochrane study is the most comprehensive review on this topic. In this review, 65 studies were compared, and it was concluded that in acute and chronic lumbar pain lacking radicular symptoms, NSAIDs were more effective than the placebo, although the NSAIDs did not perform more efficaciously than other analgesics. However, side effects were more prominent in the groups using NSAIDs. It has been reported that NSAIDs did not perform better than placebo in patients with acute radicular symptoms. In addition, it has been observed that the combined use of NSAIDs with vitamin B and muscle relaxants did not result in any additional benefits over the sole use of NSAIDs. A comparison of individual NSAIDs revealed no significant differences among them [13]. There was also no difference among NSAIDs in terms of the method of application (e.g., oral, intramuscular and topical) [14]. The gastrointestinal system is foremost affected system from the side effects of these drugs. Abdominal pain, nausea, vomiting, diarrhea, erosion of gastric mucosa, peptic ulcers and gastrointestinal bleeding constitute the most common side effects observed in gastrointestinal system. In addition, other side effects, such as acute renal failure, nephrotic syndrome, hyperkalemia, electrolyte imbalances, hypertension, cardiac insufficiency or congestive heart failure, headache, confusion, somnolence or lethargy and vertigo were also observed [15]. Limited studies comparing the effectiveness of COX-1 and COX-2 inhibitors concluded that there is no difference in their effectiveness, while they observed that stomach-related side effects were lower with COX-2 inhibitor treatment [13].

2. Opioid Analgesics

Opium was the first commonly used narcotic analgesic that dates back to the Renaissance era. Morphine, a prototype of opioids, was isolated from opium in the 19th century. Opioids function through opioid receptors [mu(v), kappa(j), and delta(c)] located at presynaptic and postsynaptic sites within the central nervous system [16]. Following the stimulation of opioid receptors, K+ is released outside the cell, and Ca+2 reuptake from voltage-dependent channels is inhibited. Hyperpolarization of membrane potentials with K+ and the inhibition of Ca+2 uptake inhibit the release of neurotransmitters and block the transmission of pain in the neuronal pathways.

Morphine and its derivatives act through mu receptors located in the periaqueductal gray substance, nucleus cuneatus and gracilis, spinal trigeminal nucleus and thalamus. The analgesic effects depend on the dosage and act through membrane hyperpolarization, inhibition of neurotransmitter release and stimulation of downstream inhibitor pathways. Mu-receptor agonists (codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone and propoxyphene) have the strongest effects. Recent studies have focused on the analgesic effects of kappa- (j) and delta- (c) receptor agonists [17,18]. These agonists can be used for those patients with hypersensitivity against the

active substance, respiratory depression, acute or severe bronchial asthma and paralytic ileus contraindications. The use of opioids with central nervous system depressants necessitates caution to prevent respiratory depression, hypotension and sedation. Acute and chronic opioid use does not cause organ failure. Constipation is the most common side effect. Tolerance for the side effects of opioid analgesics, such as respiratory depression and sedation, develops rapidly, and prescribers must consider the possible physical and psychological addiction to opioids [15,18,19].

Tramadol is an analogue of codeine and a poor mu-receptor agonist. However, the effects of tramadol on acute pain varies between 1/20th to 1/5th the effects of morphine. Tramadol also has analgesics effects in the central nervous system by inhibiting noradrenaline and serotonin reuptake [20]. Side effects due to the opioid properties include nausea, vomiting and fatigue, while those due to monoaminergic properties are headache, sedation, and drowsiness [21].

Studies on the use of opioids for non-cancer-related pain primarily focus on the addiction potential and sedation side effects of these drugs. There is a consensus on the usability of opioid analgesics in patients for whom other analgesic groups are insufficient following a detailed explanation of all of the risks [18,19]. Conversely, a Cochrane review examined three studies (908 patients) that compared opioids to placebo. Tramadol, a weak, synthetic opioid derivate, was used in these studies and was more effective than placebo [22]. A fourth study comparing opioids to NSAIDs showed that opioids did not functionally outperform NSAIDs [23].

3. Muscle Relaxants

Muscles surrounding the lumbar spine are involved in the stabilization and movement of the spine. Spasms in lumbar paravertebral muscles can cause pain and limit movements.

To interrupt the pain-spasm-pain cycle experienced by people with lumbar pain, muscle relaxants are used [15]. Muscle relaxants have different mechanisms of action and are divided into two groups, specifically, benzodiazepines and non-benzodiazepines.

Benzodiazepine muscle relaxants (e.g., diazepam and tetrazepam) have anxiolytic, sedative, hypnotic, anticonvulsant, antispasmodic, and skeletal muscle relaxant effects. These drugs bind to benzodiazepine receptors and enhance the gamma-aminobutyric acid (GABA) effect [24]. Non-benzodiazepine agents act at the brainstem or spinal cord levels, and their mechanisms of action on the central nervous system are not fully understood. Although the mechanism of action of cyclobenzaprine is not fully known, it structurally resembles tricyclic antidepressants and has predominantly sedative and anticholinergic effects. Carisoprodol and metaxalone are moderate-level antispasmodics. Carisoprodol blocks downstream reticular formation and interneuronal activity in the spinal cord. Carisoprodol is metabolized to meprobamate, which is an anxiolytic agent, and the uncontrolled use of carisoprodol causes physical and psychological addiction. Certain antispastic agents (tizanidine) demonstrated gastroprotective effects in animal studies [25]. A Cochrane review indicated that non-benzodiazepine muscle relaxants caused short-term symptomatic relief in acute lumbar pain, while in cases of chronic pain, benzodiazepines were more effective. There is no superiority among individual muscle relaxants. The use of muscle relaxants in conjunction with analgesics strengthens the effects of both drugs; however, the sedative side effects should be considered when prescribing these medications [26].

4. Antidepressants

There are studies examining the effectiveness of antidepressants on chronic pains, such as diabetic polyneuropathy, trigeminal neuralgia, tension type headache, migraine, fibromyalgia and lumbar pain [27,28]. Several mechanisms explaining the analgesic effects of antidepressants have been described. According to these studies, analgesic effects appear after the stimulation of serotonin and noradrenaline receptors. The antidepressant-related analgesia could be inhibited by naloxone, which is an opioid antagonist. Moreover, chronic antidepressant use also results in changes in the opioid receptor densities in the brain and has analgesic effects by increasing endogenous opioid levels. Antidepressants cause intracellular Ca+2 levels to decrease by binding to N-methyl D aspartate (NMDA) receptors. The inhibition of adenosine reuptake at the spinal and supraspinal levels is another analgesic mechanism of action employed by antidepressants [29].

Tricyclic antidepressants, such as amitriptyline, imipramine, and clomipramine, balance serotonin inhibition and noradrenaline reuptake. Such agents as desipramine and nortriptyline show analgesic effects by inhibiting noradrenaline reuptake [27,30].

Among the reviews on the effectiveness of antidepressants in lumbar pain, Fishbain evaluated the results of ten studies focusing on drugs inhibiting serotonin-noradrenaline reuptake and found analgesic effects in seven studies. In five studies, agents inhibiting noradrenaline reuptake were examined, and four had analgesic effects. In two studies of selective serotonin reuptake inhibitors (SSRI), no analgesic effects were observed [31].

A Cochrane review evaluated ten studies comparing antidepressants to placebo and found no additional effects over placebo for analgesia, antidepressant effects, and the functional conditions of patients [32]. Researchers concluded that the use of antidepressants in chronic lumbar pain is not indicated.

5. Anticonvulsants

Anticonvulsants reduce neuronal excitability and demonstrate analgesic effects in neuropathic pain. Gabapentin is an analogue of GABA and has an affinity to the 2-c subunits of the voltage-dependent Ca+2 channels. This drug acts as an analgesic by inhibiting voltage-dependent Ca+2 channels. Pregabalin also acts through the same mechanism [30]. Although gabapentin and pregabalin are effective on neuropathic pain originating in the spinal cord (e.g., radiculitis, arachnoiditis and postlaminectomy syndrome), they were not shown to be effective on chronic lumbar pain [33]. Gabapentin and pregabalin are effective in the treatment of post-herpetic neuralgia, diabetic neuropathy and fibromyalgia. These drugs are usually well-tolerated; however, during the early stages of their use, they may cause dizziness and drowsiness [30].

6. Physical Therapy Methods

Hot and Cold Application in Physical Therapy

Superficial heat can be applied using hot packs and ultraviolet lamps. Hot packs increase the tissue's temperature through conduction, while ultraviolet lamps provide heat through convection. Heating techniques using water, such as whirlpool baths, constitute convective heating methods [34]. Vasodilatation occurs at the superficially heated areas by reflex thermoregulation mechanisms and the direct effects of higher temperatures. Heat increases the pain threshold at the free nerve endings. Enhanced circulation by heating causes inflammatory substances, edema and exudates in the tissues to dissolve and be removed from the blood, thereby decreasing the pain. Moreover, heat is effective in reducing pain by resolving painful muscle spasms [35].

The temperature of hot packs are around 71-79 °C. However, the temperature the skin can tolerate (44 °C) should not be exceeded. Therefore, packs should be wrapped in dry towels, and the application duration should not exceed 20-30 minutes. By this method, skin heats to 42 °C, while the inner muscle temperature rises to 38 °C [36].

Ultrasound, a frequently used, deep-penetrating heating agent, disperses sound waves in the form of pressure waves in matter. Ultrasound waves used in the treatments have a frequency range of 0.5-3.5 MHz and have thermal and non-thermal effects. During the absorption of ultrasound waves by the tissue, thermal energy is released. The amount of heat generated is dependent on the absorption characteristics of the tissue, duration of application, application method and dosage. Because the difference in acoustic impedance between muscles and bony tissue is high, the amount of heat generated also is high.

The absorption capacity of adipose tissue is low, and heat would be absorbed by the bony tissue [37,34]. Applications to the surrounding area of the joints should cause a temperature rise within the joints [38]. Ultrasound waves cause bubble formations from dissolved gases in the liquid. This process is called "*stable cavitation*" or, if continuously expanding, "*unstable cavitation*." Microbubbles formed by stable cavitation become mobilized by ultrasound waves and thus increase the permeability of the cell membrane. There is a risk of cell damage with unstable cavitation. To achieve the benefits from the thermal effects of ultrasound, continuous waves should be used. For non-thermal effects, conversely, intermittent current should be applied. Ultrasound waves penetrate deeper at low frequencies and when the duration of treatment is 3-10 minutes. The duration depends on the size of the area to be treated and should be approximately 1 minute for each 10 cm2 area [34,37].

Cold treatments can be applied using ice bags or packs, which cools the superficial tissue via convection. Ice rapidly cools the skin, and the skin temperature decreases by 12-13 °C in 10 minutes. Subcutaneous tissue, conversely, cools 3-5 °C during this period, while the intramuscular temperature decreases 1 °C or less [34].

Cold treatments cause vasoconstriction and slows down metabolic activity. During cold applications, reflex vasodilatation, known as the "*Hunting reflex*," prevents further heat loss. Inflammation is controlled by vasoconstriction and decreases with phagocytosis. Cold applications reduce muscle spasms by inhibiting the transmission in gamma nerve fibers. With cold application, neural transmission slows, thereby providing analgesia [34,35].

A Cochrane review evaluated the effects of superficial hot and cold treatments in patients with lumbar pain in 11 studies. The results describe moderate efficacy for heat treatments on acute or subacute lumbar pain, but there was insufficient data on the efficacy of cold treatments to draw concrete conclusions [39].

7. Transcutaneous Electrical Nerve Stimulation (TENS)

The development and application of transcutaneous electrical nerve stimulation (TENS) is based on the "gate control theory" introduced by Melzack and Wall [40]. According to this theory, stimulation of A-beta fibers by the primary sensory afferent nerves results in the stimulation of inhibitory neurons located at the substantia gelatinosa of the anterior horn in the spinal cord, thereby preventing the transmission of painful stimulants to A-delta and C fibers [40]. Furthermore, supraspinal mechanisms that affect the endogenous opioid system have also been described [41]. Two reviews by Tulder [42,43] emphasized the uncertainty of the effectiveness of TENS on lumbar pain. A Cochrane review demonstrated similar results [44]. TENS has more than one application method, depending on the current frequency, amplitude, current range and waveform. Among these methods, the conventional TENS and low-frequency TENS, which resembles acupuncture, are applied most frequently [44]. Studies examining the effectiveness of these two types of TENS did not reveal any significant differences between the methods [45,46].

8. Manipulation

Manipulation is the manual, controlled, and sudden-thrust movement performed within the limits of anatomical joint movement range and exceeding the limits of passive movement. There are many defined manipulation techniques, including thrust techniques, positional techniques, counterstrain, functional techniques, soft tissue techniques, muscle energy, myofascial release and craniosacral manipulation [47,48].

The restriction of normal joint movement is a result of shortened joint capsules or ligaments. Inflammation and edema, conversely, lead to pain and tonus increase. Thrust is used to treat restriction, while manipulation is effective in treating segmental movement limitations. Although the mechanism of action of manipulation is not clearly known, many hypotheses have been proposed. Dense proprioceptive and kinesthetic stimulation of the spinal cord during manipulation creates a blockade against pain transmission. With manipulation, the vertebra attains its normal symmetric position and abnormal proprioceptive stimuli decrease. Manipulation also stretches the posterior longitudinal ligament, applying pressuring against herniated disc and reducing pain. In slow, progressing degenerative conditions that lead to vertebral dysfunction, "*postural syndrome*" characterized by sporadic pain, dysfunctional syndrome characterized by vertebral mobility loss and insufficiency syndrome, including disc anomalies, can occur [47]. Another hypothesis suggests the presence of nuclear fragments in annular fissures cause dysfunction by blocking mobile segments between the discs. Manipulation relocates the fragments and corrects the dysfunction of the spinal segments [49].

Thick and solid meniscoid structures in the facet joints become compressed in the joints during movement, and the stimulation of mechanoreceptors in the capsule results in muscle spasms. Manipulation separates the two joint surfaces and releases the structures [47,49]. A Cochrane review found that the effects of spinal manipulative treatment exceeded those of the placebo in acute and chronic lumbar pain cases; however, the review did not reveal that manipulation yielded significantly different results from those of the other conservative treatment methods [50].

9. Acupuncture

Traditional Chinese medicine dates back to 3,000 years ago and is based on the "power of life" theory, which supports physiological living. The power of life, "qi," divides the body into 12 meridians, and it is believed that illnesses are the consequences of instabilities in energy flow and inappropriate distribution of energy. The use of acupuncture in the treatment of lumbar pain and other disorders have been approved by the *National Institute of Health* (NIH) [51].

Acupuncture is applied by inserting gold, silver or stainless-steel needles into certain areas of the skin. Stimulation of the area can be performed either rotating the needles by hand or by applying electrical current [52].

Melzack and Wall's [40] "gate control theory" and the meridian theory attempted to explain acupuncture's mechanism of action.

A Cochrane systematic review of 35 studies examined the effectiveness of acupuncture for lumbar pain. The lack of evidence restricted studies investigating acute lumbar pain; however, acupuncture was more effective than the placebo in certain cases of chronic lumbar pain. Although acupuncture did not surpass other conservative or alternative treatments, when applied in conjunction with other conservative treatments, this approach relieved pain and contributed to increased function [53].

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