

Medical cannabinoid in pain management after spinal cord injury

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Abstract

After spinal cord injuries pain remains chronically in many cases and it and its secondary complications delay their recovery and induce poor prognosis in them. Some drugs such as anticonvulsants (gabapentin, pregabalin), tricyclic antidepressants (amitriptyline, desipramine) and serotonin-noradrenaline reuptake inhibitors (duloxetine) are recommended as the first-line treatment for chronic pain and topical lidocaine (which only acts locally), opioids are additionally recommended as second options. However, chronic pain syndrome remains as a common complaint in many SCI-patients. In recent years several alternative approaches such as Botulinum toxin A therapy and medical cannabinoids have been studied and recommended more in clinical practice. Actually medical use of cannabinoids are allowed in some countries and applied widely. Medical cannabinoids have been known as a safe and effective therapy and showed the positive effects in pain reduction and improvement of life quality in SCI patients in clinical studies. Further discussion is necessary for the safety and effective application of medical cannabinoids.

Keywords: spinal cord injury, pain, cannabinoid

Pain after spinal cord injury

Every year, as many as 500,000 people suffer a spinal cord injury [1]. Most of these are caused by trauma and followed by complete or incomplete, para- or tetraparesis, incontinence, breathing problem, spasticity, other secondary complications such as muscle atrophy, pressure sores, infections. The prognosis of SCI are different from recovery to permanent severe disability, depending on the extent of injuries, and pain is one of the problems which were often complained among them [2-4].

65 -85% of SCI patients have pain [4], which is induced mostly by musculoskeletal, neuropathogenic, visceral triggers, and neuropathic pain of them often remains chronically with high percent. The secondary complications such as spasticity, pressure sores, degenerative

changes in musculoskeletal organs are also associated with chronic pain. Unfortunately in some cases, painful conditions persisted for their life, and it affects family interactions, social situations, community participation and overall quality of life. It can become the one of the health concerns of SCI patients [5-9].

The development of chronic pain after SCI

The chronification of nociceptive pain after SCI begins with the activation of receptors (nociceptors) sensitive to noxious stimuli and prolonged or intense exposure to these stimuli, then peripheral sensitization involving a shift in the activation threshold of nociceptors and upregulation of voltage-gated sodium channels. The increased action potential firing and transmitter release in the dorsal horn of the spinal cord induces heightened excitability in the

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injured location of the spinal cord and central sensitization with exaggerated response to painful stimuli (hyperalgesia) and pain elicited by normally non-painful stimuli (allodynia). Which is called pain hypersensitivity, it makes abnormal changes in the brain over time and pain „learning“ [10-14].

The development of chronic neuropathic pain is however so different. Stimulus-independent activity evoking in injured nerve fibers after SCI induces active microglia at the lesion site in the dorsal root ganglion and in the dorsal horn of the spinal cord, which release chemical mediators modulating the activity of neuron, such as brain-derived neurotrophic factor (BDNF). BDNF reduces the inhibitory effect of γ -aminobutyric acid (GABA) and glycine and it tolerates abnormal input from the lesioned nerve throughout activity of polysynaptic connections in the dorsal horn, then central sensitization occurs. It aggravated by downregulation in transmitter uptake and increased glutamatergic transmission causes excitotoxic cell death, reducing the number of inhibitory interneurons. This pronounces a imbalance between inhibition and excitation by descending pathway from the brainstem [13-15]. The complexity of chronic pain mechanisms make a major therapeutic challenge in chronic pain management after SCI.

Pain mangement in SCI patients

Pharmacological therapy is mainly recommended in the mangement of chronic pain in SCI patients. Anticonvulsants (e.g. gabapentin, pregabalin), Tricyclic antidepressants (e.g. amitriptyline, desipramine) and serotonin-noradrenaline reuptake inhibitors (e.g. duloxetine) are recommended as the first-line treatment. topical lidocaine (which only acts locally), opioids (e.g., morphine) are recommended as second-line treatment options. However, many patients complain inadequate effect under these drugs and require medical help in order to control severe chronic pain syndrom. In recent years botulinum-Neurotoxin (BoNT) and cannabinoids can be also considered as alternative options for them which have already applied widely in clinical practice.

As the medical use of cannabinoids is allowed in some european and south-american countries, it is growing evidences for cannabinoids to use in clinical practice. [15-21]

Medical cannabinoids

Cannabinoids are chemical compounds found in cannabis plants. They may act on cannabinoid receptor type 1 and type 2 (CB1 and CB2 receptor) which are distributed in the peripheral and central terminals of primary afferents, peripheral ganglia (e.g. dorsal root ganglia), neurons in the spinal cord and brainstem, pain-regulatory circuits in the brainstem (e.g., periaqueductal gray) and different brain regions. CB1 receptors are predominantly expressed in presynaptic neurons and binding cannabinoids with cannabinoid receptors induces commonly the inhibition of adenylyl cyclase in the synthesis process of intracellular cAMP and the down-regulation of intracellular cAMP-dependent enzymes. It causes the shortening the duration of presynaptic action potentials by the prolonging the inwardly rectifying and A-type outward potassium channels and inhibition of the presynaptic Ca^{2+} influx through voltage-gated Ca^{2+} channels, and it results the reduction of release of excitatory neurotransmitters. CB2 receptors are predominantly expressed in immune cells such as mast cell and microglia. Through their inhibition of adenylyl cyclase via their $\text{Gi}/\text{Go}\alpha$ subunits, cannabinoids cause the reduction in the binding of transcription factor CREB (cAMP response element-binding protein) to DNA, and it can result the inhibition the release of pro-inflammatory mediators. Cannabinoids can also lead the inhibition of T cell receptor signaling through the phosphorylation of leukocyte receptor tyrosine kinase at Tyr-505 [22-27].

On these mechanisms, at the peripheral sites in pain pathway, cannabinoids cause the reduction of release of pre-synaptic neurotransmitters and inflammatory mediators via activation of CB1 and CB2 receptors, leading to decrease the subsequent sensitivity of primary afferent fibers and inhibit unnecessary local immune actions. At the central nervous system, cannabinoids induce the suppression of inhibitory GABAergic inputs onto output neurons which

constitute the descending midbrain periaqueductal grey-rostral ventromedial medulla-spinal pathway (PAG-RVM-spinal pathway) through the activation of CB1 receptors in GABAergic neurons and it may elicit analgesia by inhibit ascending nociceptive transmission at the spinal cord dorsal horn. It may have possible therapeutic roles in the treatment of SCI-related pain [28-33].

The phytocannabinoid tetrahydrocannabinol (THC) (Delta 9-THC or Delta 8-THC) and cannabidiol (CBD) are mostly applying cannabinoids in clinical practice and they are isolated from cannabis plants or are manufactured artificially. THC has been known to show the antiemetic, anxiolytic, appetite-stimulating, analgesic, neuroprotective and psychoactive effects through the activation of CB1 receptors in neurons. CBD is introduced to support the pain relief effects of THC and combination of THC and CBD (e.g. Sativex® spray) are thought to provide activity greater than that of the individual components. The medical use of cannabinoids has been limited because of side effects including sedation, motor impairment, addiction and cognitive impairment. Many studies have discussed on the safety and the efficiency of medical cannabis in many clinical status such as Parkinson disease, Alzheimer's disease and multiple sclerosis [30, 34-36].

Cannabinoid therapy in SCI patients with pain

Actually, cannabinoid has been reported as a helpful approach for the management of chronic pain in SCI patients. Drossel et al. showed in their study with 244 SCI patients that cannabinoid reduced pain in 70.4% of them and improved spastic movement disorder, which is often related with secondary pain syndrome or aggregation of pain syndrome in 46.3% [34]. In other studies, cannabinoid therapy had also the positive effect with relief of chronic pain. Additionally, cannabis improved other symptoms such as spastic movement disorder, sleep disorder, anxiety and loss of appetite [38-40].

It also suggested that MC could be either as adjuvant therapy or as monotherapy. One survey showed 81% of patients had positive effect as MC monotherapy for chronic pain [41]. In other survey, 63.3% reported that cannabis should

better effects than other classic analgetics or pain modulators, 10.20% answered that only cannabis offered them relief of pain. Although the relief of pain by MC was often short-term effect e.g. for hours, it was helpful in their daily life and social participation [9, 42, 43]. The adjunctive MC therapy with other medications such as opioids showed more effective in some patients [44].

However, MC showed no effect to control pain in some patients [38, 45].

In most of studies, cannabinoid therapy was reported as a safe therapy. In few studies the side effects of MC such as fatigue, dizziness, constipation, drowsiness, lack of energy occurred in some patients, but there were no life-threatening side effects and their prevalence was significantly low compared to other medication such as opioids [38, 46].

Overall, cannabinoid therapy is a safe and effective approach for the management of chronic pain following spinal cord injury, especially in SCI patients with severe pain non-manageable by other therapies and it can be applied as either a monotherapy or combined use with other medication. Although cannabinoid therapy showed several side effects and had no effects in some SCI patients, it is recommended as a safe therapy for chronic pain and in further studies it is necessary to avoid possible side effects and to achieve better effect of them. For instance, the appropriate ratio of THC versus CBD as well as their dosages can be further discussed.

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