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Focused Review

COVID-19 Pandemic: Implications on Interventional Pain Practice—a Narrative Review

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Background: The COVID-19 pandemic has emerged and has challenged us to look for alternatives to bring about a paradigm shift in interventional chronic pain management. As the disease lowers the body's immune system, the use of medications that suppress the immune system are not recommended during the COVID-19 pandemic.

Objective: The purpose of this study was to review medications other than steroids used for interventional pain management and the emphasis on mitigation of the untoward consequences of steroid injections on the immune system during the COVID-19 pandemic.

Literature Search: The literature was searched for articles in English with key words COVID-19, immunity, steroid for pain management injections with steroid, local anesthetics, dextrose water, normal saline, pain and genetic medicine, pain, and regenerative medicine. The sources of articles were PubMed, Embase, and open Google search.

Literature Review: The medications used for interventional pain management include steroids and opioids. The side effects of these medications are well known but have never been looked at as critically as they are now. Many other medications have been used for interventional pain procedures to relieve pain, such as dextrose water, normal saline solution, local anesthetics, and many adjuvants. Regarding regenerative therapy, despite plenty of evidence in literature, we have not yet considered it as a routine therapy for chronic pain injections. It is now time to move on beyond steroids and consider other types of medications and treatment options.

The use of these medications in clinical practice is less auspicious, and thus more research is needed on the practical applications. Further areas for research include studies to determine definitive efficacy and safety assessment and determine whether or not the analgesic effects of these drugs are duration or dose-dependent. The optimal identification of candidates, volume, concentration, and intervals of injection are essential for routine application in interventional chronic pain practice.

Conclusions: The future of interventional pain practice is trending toward regenerative medicine and genetic research. Numerous scientific studies have been conducted to investigate the genetic basis of phenotypic variability in individuals with different ethnic groups in terms of susceptibility to chronic pain, as well as response to treatment for the personalized medicine model. Despite the preliminary data on genetic variations, there is no evidence for the use of a pharmacogenomics-based approach to personalized medicine for patients with chronic pain. The field of medicine therefore needs further research in pharmacogenetics, including large-scale prospective studies that focus on pain pathways. However, recent research, including larger studies and larger-scale genomic perspectives, may yield more promising findings in the future. The COVID-19 pandemic proved the need for medications with the most impact and least complications.

Key words: COVID-19, steroid, pain injections, chronic pain, immune system, regenerative medicine

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COVID-19, a disease caused by coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2), is spreading as a rapidly transmissible disease that has now affected more than 100 countries. The disease is spread primarily through large respiratory droplets, although the possibility of other transmission routes cannot be ruled out, as the virus is found in the feces and urine of infected people (1).

COVID-19 pandemic is a new crisis that has shocked the world. We are facing a disease about which we do not have much information. Every day new information is presented but we are still at the beginning of the road. It is clear that all branches of medicine need to update patients' needs and treat them in the face of a new crisis. Little is known about chronic pain and COVID-19. We need to be prepared to treat patients with chronic pain in this viral crisis because the future world, as we have seen, is the world of fighting with viruses. We need to be prepared and change the treatment paradigms based on new considerations from now on. Chronic pain is the leading cause of disability in the world and is associated with many psychological comorbidities. Pain is one of the major health issues in the world, and access to pain treatment is a fundamental human right. Global crises exacerbate the risk of chronic pain through the increasing social stress. Most patients with chronic pain have accompanying disabilities that put them at risk for COVID-19. People over the age of 65 years and people with lung disease and weakened immune systems are at a higher risk (2).

Pain and the immune system are closely related. The connection between the nervous system and the immune system plays a key role in causing chronic pain. Immune cells and their products are involved in inflammatory pain and neuropathy. The effects of chronic pain on the immune system are very complex, including suppression of the immune system reducing the ability to fight the virus. However, most of the risks for patients with chronic diseases are mainly related to immunosuppressive drugs, and not the disease itself (3).

The inadequate or lack of treatment for chronic pain in both short and long term will have consequences on patients and health care systems. Therefore the task of pain specialists in this time of crisis is enormous. Drugs that greatly suppress the body's immune system must be set aside as they put patients at greater risk of infection, and sometimes may make it difficult to diagnose because patients may not show natural symptoms of infections, such as high fever (1). The most important medications used in interventional pain procedures are steroids, and the dangers of using steroids have been discussed but have never been taken as seriously as they are now (4). It is necessary to control pain without weakening the immune system and increasing the risk of COVID-19.

Many other medications have been considered to relieve pain, but they have not been routinely used for pain injections. In this article, lesser-used drugs and their practical implications for pain injections will be introduced and the importance of personalized medicine will be discussed. Further research in this area will be pointed out as the future of pain specialty, including the clinical application of genetics in chronic pain management.

Discussion

COVID-19 and Immunity

What are the specific features of the virus that should be considered during pain injecting? Because of the weakening effects of the virus on the immune system, patients with chronic pain are more likely to develop COVID-19 as a consequence of chronic pain itself or after therapeutic steroid injections. Lymphocyte subsets play an important role in regulating the body's cellular immunity, and lymphocytopenia is one of the most prominent indicators of COVID-19. T cells and NK cells are reduced in patients with COVID-19. In addition, memory T helper cells and regulatory T cells were clearly reduced in severe cases. Immunohistochemical staining showed that CD4 + T cells and CD8 + T cells in the spleen and lymph nodes were reduced, and CD4 + T, CD8 + T, interleukin (IL)-6, and IL-10 are statistically significant in the rate of immune suppression between mild and severe disease. Secondary lymphoid tissue is lost in patients with COVID-19. Spleen atrophy and lymph node atrophy are seen with a decrease in the number of lymph nodes. There are two possible reasons for the loss of the immune system in patients with COVID-19. Lymphocytes are directly attacked by the virus or indirectly damaged by a cytokine storm. The virus infects target cells via angiotensin–converting enzyme 2 (ACE2), which is the receptor for SARS-CoV-2. In the human natural lung, ACE2 is expressed in type I and II alveolar epithelial cells, and there is no ACE2 expression on lymphocytes as it is assumed that lymphocytes may have been destroyed by cytokine storm (5,6).

Steroids and COVID-19

Patients with chronic pain may take oral steroids or inject steroids for a variety of musculoskeletal conditions or spinal pain. Although steroids are used in almost every injection, the reasons for their use are unclear. It is not clear whether steroids have a direct effect on causing or transmitting pain. There is empirical evidence to suggest suppression of ectopic discharge in neuromas (7). Although studies showed the efficacy of steroids for the treatment of neuropathic pain, however, there is a contradictory effect of increased pain in some patients (8).

Epidural steroid injection (ESI) for back pain, with or without radicular component, is the most widely used method in the world. Despite the extensive literature on the subject, there is still considerable debate about their safety and efficacy. Theoretically, the risk of infection is higher in immunocompromised patients. Cortisol suppression depends on the type and dose of steroid used. The systemic effects of injectable steroid appears when the dose of steroid exceeds the rate of endogenous steroid production. Cortisol suppression may increase the risk of infections. There is no clear recommendation for spinal injections for patients who are immunosuppressed. There is some information about the optimal time to perform a procedure, but there is no clear evidence of a causal effect between spinal injections and infections in immunocompromised patients. However, it is possible that steroids may increase the risk of infection in these patients, and steroids should be used with caution (9). Because of the side effects of steroid injections, it is always important to pay attention to safety tips before steroid injection, especially in high-risk patients with an underlying disease. Concerns about major neurologic damage after steroid stimulation have been suggested to prevent these complications, including by reducing the dose of steroids for safety reasons (10). Reducing the dose of corticosteroids can increase the safety of ESI without compromising pain relief (11). The ideal dose of corticosteroids in epidural radiculopathy management is still unknown. In a study to determine the effective dose of steroids for transforaminal epidural steroid injections (TFESI) to reduce pain in patients with lumbar radiculopathy, a total of 160 patients received 2 epidural injections of 5, 10, 20, or 40 mg triamcinolone at 1-week intervals via a transforaminal approach. Patient satisfaction rate and verbal numerical ranking scale in pretreatment were assessed 1 week and 2 weeks after the first TFESI. The authors recommended based on the results of this study for patients with lumbar radiculopathy to use the triamcinolone 10 mg in TFESI (12).

Evaluation of the efficacy and safety of epidural dexamethasone and methylprednisolone in the treatment of lumbar radiculopathy showed that the nonparticulate steroid is close to the safety and efficacy of the particulate steroid in the treatment of lumbar radiculopathy (13). The effect of ESIs and nonsteroidal epidural injections and placebo for the treatment of low back and neck pain were compared in a review article based on randomized controlled trials (11). The treatment group received ESIs or other analgesic and the control groups received either an epidural injection without a treatment drug, or a nonepidural injection. The study showed epidural nonsteroidal injections may provide an improved benefit compared with nonepidural injections (11). A systematic review that evaluated the clinical benefits of steroids used in conjunction with local anesthetic (LA) and LA alone in chronic noncancer pain management showed LAs alone appear to reduce pain without the use of steroids (14). It is important to note that for many injections, such as trigger point injections, there are no benefits to adding steroids (2,15). Considering cortisol suppression depends on the type and dose of steroids as mentioned earlier, the use of a short-acting steroid with the lowest effective dose or use of LA alone without steroids or using another analgesic is more reasonable during COVID-19 time.

LAs and COVID-19

LAs are often used in chronic pain injections. Even LAs alone appear to reduce pain without the use of steroids (14). LAs block voltage-gated sodium channels, and thus prevent the production of action potentials and its dissemination along the nerve. In chronic pain injections, unlike regional blocks, only pain-selective nerve blocks are considered to block. A concentration of LA is selected that is sufficient to block specific nerve fibers of smaller sizes (A-delta or C-fibers), not motor nerves of larger diameter (A-beta) (16).

There is a distinct difference between local anesthesia in motor versus sensory blockade, for example, bupivacaine is generally more effective for sensory/nociceptive block than the motor block, although this does not always follow the size of the nerve, and sometimes the motor fibers are blocked before the nociceptive fibers. Genetic studies have shown that subtype Na(v)1.7 channel has the ability to block the transmission of pain sensation alone (17).

Research is ongoing to find a drug that is selec-

tive for C-fibers. The subgroups of the sodium channel and the transient receptor potential (TRP) agonists and antagonists have been shown, as well as the composition of TRP vanilloid receptor 1 (TRPV-1), agonists with permanently charged large LA molecules that could selectively block C fibers (18). Nociceptive selective block of LA is valuable in chronic pain injections, especially in the COVID-19 pandemic, in which maintaining a patient's well-being and avoiding respiratory depression are both important. Until then, it is best to use the lowest volume and lowest effective concentration of anesthetics for pain injections. Sometimes, the combination of anesthetics is effective in reducing their side effects (19,20).

Dextrose Water and COVID-19

Dextrose water injections have been reported to reduce pain, including chronic low back pain, neurogenic pain, hyperalgesia, and allodynia. The use of dextrose in nerve blocks may facilitate diagnostic and therapeutic injections while preventing lidocaine toxicity (21). Epidural injections of D5W have resulted in persistent pain relief after injection and significant clinical improvement in pain and disability (22,23). The persistent pattern of pain relief after dextrose injection shows the sensorineural effect of dextrose in neurogenic pain (24). It increases the permeability of the peripheral cell membrane for lidocaine and may also directly affect nerve conduction (25). The main reason for the analgesic effect of D5W is not yet known, but it is hypothesized that dextrose acts at the level of pain receptors, especially the TRPV-1, which plays a key role in the development of allodynia and hyperalgesia in patients with chronic neuropathic pain (26,27). In addition, increasing extracellular dextrose may increase the polarization of C-fibers and reduce their firing level and pain perception (28). Dextrose injections may provide analgesia by correcting local glycopenia (29).

Prolotherapy, which involves injecting 12.5% to 25% dextrose into joint spaces and into soft tissue connections, creates an inflammatory reaction on the tissue surface in favor of anabolic processes and has many therapeutic effects, however, low-concentration D5W does not appear to have inflammatory properties. Hypertonic dextrose injections are effective in treating and reducing the pain of chronic painful musculoskeletal diseases, such as osteoarthritis of the joints (level A evidence for knee osteoarthritis, level B evidence for hand osteoarthritis), tendinopathy of the rotator cuff, Achilles tendinopathy and fasciopathy, epicondylitis of the elbow, dysfunction of the sacroiliac joint, and temporomandibular dysfunction. Hydrodissection with dextrose by injection adjacent to peripheral nerves release peripheral nerves from their encasing fascia and reduce pain. Peripheral perineural injection of dextrose 5% to 20% also reduces the neuropathic pain by itself (22,30).

It seems that paying attention to the analgesic effects of dextrose is very useful for chronic pain injection during the COVID-19 pandemic. There is no report of detrimental effects of dextrose on the immune system, patient's respiration, hemodynamics, or movement after injection, which is especially crucial in high-risk patients. Using dextrose alone or combined with LA is a good option in the COVID-19 crises, and more research in this field is thus needed.

Normal Saline Solution and COVID-19

Studies have shown that normal saline (NS) solution, which is used as a placebo, may have analgesic effects. Epidural injection of NS solution after spinal anesthesia will cause more analgesia than spinal anesthesia alone (31). NS solution alters the abnormal joint environment, and pain is relieved by injecting large amounts of NS solution in joints with osteoarthritis probably by diluting inflammatory cytokines. The arthrocentesis by NS solution is an effective way to eliminate synovial fluid cytokines in temporomandibular joint dysfunction (32). Similarly, pain decreases after injection of lidocaine or NS solution in patients with fibromyalgia (33). Intraarticular injection of NS or NS with morphine both reduce pain (34).

The COVID-19 pandemic and the limited use of opioids and steroids necessitate reconsideration of new drugs for pain injection. We need to pay more attention to the analgesic effect of NS solution. It seems that diluting drugs with NS solution is better than distilled water for the pain injection because of the possibility of analgesic effects of NS solution.

Adjuvants and COVID-19

The adjuvants medications along with local anesthesia may initiate and accelerate the duration of pain and counteract the side effects of local anesthesia. These drugs are mostly used in regional anesthesia, although there are many articles about their use in chronic pain injections. However, the COVID-19 pandemic and the limited use of opioids and steroids necessitate reconsideration of these drugs with further studies on them. Adjuvants are divided into opioid and nonopioid

drugs (e.g., epinephrine, clonidine, dexmedetomidine, neostigmine, adenosine, magnesium, hyaluronidase, etanercept, and tocilizumab). A combination of drugs reduces the dose of both classes of drugs and the likelihood of side effects associated with either drug (35). The analgesic properties of epinephrine is mediated by the perineural vasoconstrictive and intrinsic antinociceptive properties mediated by alpha-2 adrenoceptor activation (36). Epinephrine with short-term and moderate LA shows more analgesic action (37).

Alpha-2 adrenoceptor antagonists (clonidine, dexmedetomidine) are widely used and have a satisfactory analgesic effect on neuraxial and peripheral blocks. Dexmedetomidine is 7 times more selective than clonidine on alpha-2 receptor agonists and it is superior as an adjuvant for epidural or intrathecal administration and some nerve blocks (38). This effect appears to be deeper in C-fibers, making them more sensitive to pain. In neuraxial blocks, it has an effect on blocking the sympathetic outflow along with peripheral nerve blocks, and it prolongs the analgesic duration by hyperplasia of the cyclic nucleotide-gated cation channels (39). Adding sodium bicarbonate to an LA solution containing clonidine increases the analgesic duration (40). Intrathecal neostigmine causes analgesia through the muscarinic receptor-mediated mechanisms (41). Magnesium sulfate is an N-methyl-d-aspartate receptor antagonist and voltage-gated calcium inhibitor. Intrathecal administration of magnesium sulfate suppresses neuropathic pain impulses, enhances opioid analgesia in animals, and increases the duration of peripheral nerve block analgesia without any adverse effects (42,43). Epidural injection of hyaluronidase, an enzyme that hydrolyzes glucosamine bonds between hyaluronic acid and connective tissue, alters the permeability of connective tissue, reduces viscosity between cells, and decreases edema and pain (44).

Cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF-α), are strongly associated with radicular pain and are a trigger for spinal stenosis. IL-1β, IL-6, and TNF-α have a toxic effect on the dorsal root ganglion. The concentration of IL-6 in articular cartilage and synovium of the facet joint is also high. The epidural injection of the anti-IL-6 monoclonal antibody (tocilizumab), reduces radicular pain, numbness, and back pain without side effects. It can also be helpful in treating rheumatic joint pain. TNF-α inhibitor may be a useful tool for treating radicular pain caused by spinal stenosis, and epidural administration of TNF-α inhibitor reduces pain with no side effects (45-47). More information is needed on the effectiveness of these drugs in increasing the duration of local anesthesia or selective sensory blockade before the widespread use of these drugs in chronic pain injections.

Regenerative Medicine and COVID-19

Regenerative medicine is a new field of medicine that seeks to absorb and strengthen the body's innate ability in treating its own pathology to repair damaged tissue using autologous or allogeneic biologics. Mesenchymal stem cells and platelet rich plasma (PRP) are effective in treating discogenic pain, radicular pain, facial joint pain, and sacroiliac joint pain. There is level III evidence for lumbar epidural, and level IV for facet joints and sacroiliac joint injection (48,49). It is also an effective treatment for osteoarthritis of the knee and pelvis by improving the clinical condition and reducing pain. Clinical trials have shown the effectiveness of PRP in treating muscle, bone, and cartilage damage (50,51).

Growth factors in PRP have significantly improved tendon injuries, such as tendinopathy. PRP can be a better alternative to tendinopathy than steroid therapy. The positive effects of PRP on tendons are secondary to increasing the proliferation of tendon cells, increasing the expression of anabolic genes and proteins, and reducing tendon inflammation (52). PRP and bone marrow aspirate concentrate are among the orthobiologic therapies used as alternatives to current therapies for muscle, bone, and cartilage injuries. In particular, osteochondral lesions, the defects in cartilage surfaces are often associated with traumatic origin (joint dislocation, ligament rupture, meniscus rupture). These therapies increase the number of biologically active cells or molecules in the tissue, which lead to regeneration and repair (53). A regenerative treatment based on a combination of intraosseous and intradiscal platelet-rich growth factors have been proposed for disc degeneration with level III evidence (54).

Further research on regenerative therapies seems necessary during the COVID-19 pandemic to be a good alternative to steroids and opioids.

Future Trends

One of the most important issues in interventional procedures for chronic pain management is the use of medications, such as steroids, opioids, and nonopioids. However, because of the wide variety of interactions between individuals in response to treatment and side effects, finding the right drug and the right dose for each patient with the help of genetic data for achieving

the best therapeutic response with the least side effects is crucial, especially during the pandemic. Numerous scientific studies have been conducted to investigate the genetic and epigenetic basis of phenotypic variability in individuals and different ethnic groups in terms of susceptibility to disease, as well as their response to the treatment. Personalized medicine is a patient-specific way to identify the optimal treatment for each patient. It is mainly measured by biologic markers and each person's genetic profile for the purpose of focused treatment on each individual to improve health benefits (55).

Neurotransmitters released after stimulation of sensory receptors (e.g., catecholamines, GABA, serotonin, and the proteins, which are responsible for the release of these neurotransmitters) are candidate genes for chronic pain management, and variety in these genes is a cue not only in understanding pain but also in treating pain. TRPV-1 is a protein that acts as a capsaicin receptor. Toll-like receptor 4, however, is a receptor for cellular signaling and inflammatory responses, both of which are used as drug targets in reducing pain (56,57).

Genetic changes in P-glycoprotein are known to be effective in reducing adverse drug reactions and increasing the analgesic effect. Most clinical information is on low plasma concentrations of an active mu-opioid agonist metabolite, which is directly related to reducing pain sensation in individuals. Spinal pain with a specific drug in the presence of allele C3435T has been associated with increased respiratory depression and the need for oxygen. Genetic testing of CYP2D6 before prescribing codeine can improve the safety of pain management and avoid the negative consequences of treatment. Tricyclic antidepressants, commonly used to pain control, are also metabolized by CYP2D6, and CYP3A4 plays an important role in the metabolism of some opioid drugs. TNF-α is effective in hyperalgesia sensation of chronic disease, and its allele α-308 G/A is associated with higher pain perception (58,59).

Of the 3 haplotypes containing alleles rs6269, rs4633, rs4818, and rs4680, some haplotypes have been associated with various phenotypes of low-pain sensitivity, moderate-pain sensitivity, and high-pain sensitivity. Moderate-pain sensitivity haplotypes have been associated with further recovery and pain relief after lumbar surgery in patients with disc herniation. The COL9A2 allele, which encodes a collagen chain, has been associated with a 4-fold increased risk of annular tears and a 2.4-fold increase in the risk of degenerative disc disease and disc herniation (60). Genetic research promises more selective drugs for the treatment of inflammatory and neuropathic pain in the future.

Conclusions

During the COVID-19 pandemic, it is preferred not to use steroids, or use short-acting steroids with the lowest possible therapeutic dose, or replace them altogether with another analgesic. It seems that we need to pay more attention to safer analgesics in the times of COVID-19. Diluting drugs with NS solution are better than distilled water for the pain injection because of the safety and analgesic efficacy of NS solution. Dextrose does not have a detrimental effect on the immune system and does not exacerbate the viral disease. It is a safe drug with no effect on the patient's respiration, hemodynamics, and movement. Using dextrose alone or combined with LAs is a good option during the COVID-19 pandemic. Using nociceptive selective block of LA is clearly valuable in chronic pain injections during the pandemic, in which maintaining a patient's well-being and avoiding respiratory depression are both important. It is best to use the lowest volume and concentration of LAs for pain injections. Often, the combination of anesthetics is more effective in reducing their side effects. Using adjuvants along with local anesthesia may enhance the duration of pain and counteract the side effects of local anesthesia. Regenerative medicine is a safe and effective therapy that strengthens the body's innate ability in treating its own pathology to repair damaged tissue using autologous or allogeneic biologics and could be a good alternative for steroids and opioids.

Although recent research, including larger studies and larger-scale genomic perspectives, may yield more promising evidence in the future, the COVID-19 pandemic has driven the need to consider medications with the most therapeutic effects and least complications. The field of pain medicine needs further research in pharmacologic studies, especially on pharmacogenetics, including large-scale prospective studies that have a greater focus on pain pathways.

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