Geleneksel ve Tamamlayıcı Tıp Dergisi
Journal of Traditional Medical Complementary Therapies
J Tradit Complem Med. 2021;4(3):394-9

DERLEME REVIEW

DOI: 10.5336/jtracom.2020-79906

Effects of Local Anesthetics on Viruses from a Neural Therapy Perspective

Nöral Terapi Perspektifinden Lokal Anesteziklerin Virüsler Üzerindeki Etkileri

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ABSTRACT Viral infections have become one of the major health problems of today's world. Especially the current coronavirus disease-2019 outbreak, causing systemic complications and mortality, has led to a serious pandemic worldwide. The disease has a wide clinical spectrum ranging from asymptomatic mild form to multiorgan failure and death. Although there is no treatment for coronavirus infection, some medications are used to suppress the inflammation. For this reason, the anti-inflammatory treatments have drawn attention to itself. Local anesthetics which are anti-inflammatory drugs have been effective in several steps on inflammatory cascade. In our daily practice, one of the treatment methods with local anesthetics is neural therapy which is special injection techniques (local, segmental, ganglion and interference area injections) and are applied to certain parts of the body for diagnosis, treat inflammatory diseases, pain and dysfunctions. With the local anesthetic usage, the autonomic nervous system is regulated via inhibition of abnormal stimuli transmitted by this system and controlling information pathways between cells. At the same time, the antiviral and anti-inflammatory effects of local anesthetics have been shown in various studies. It is considered that local anesthetics have anti-inflammatory effects by regulation of synthesis and release of anti-inflammatory mediators and antiviral effects by releasing of free radicals from lysozyme and inhibiting of membrane ATP-ase. In this review, we aimed to discuss the effects of local anesthetics and neural therapy on viral infections in the light of the literature and evaluate their possible beneficial effects on coronavirus infection.

Keywords: Neural therapy; local anesthetics; coronavirus; COVID-19

ÖZET Viral enfeksiyonlar, günümüz dünyasının önemli sağlık sorunlarından biri hâline gelmiştir. Özellikle mevcut koronavirüs hastalığı-2019 salgını, sistemik komplikasyonlara ve mortaliteye yol açarak, dünya genelinde ciddi bir pandemiye neden olmuştur. Hastalık, asemptomatik hafif formdan, çoklu organ yetersizliğine varan ve ölümle sonuçlanabilen geniş bir klinik spektruma sahiptir. Koronavirüs enfeksiyonunu tedavi edebilen bir ilaç henüz bulunmamakla beraber, tedavide kullanılan ilaçlar, inflamasyonu baskılamaya yöneliktir. Bu nedenle de inflamasyona karşı kullanılan tedaviler dikkat çekmektedir. Lokal anestezikler, inflamatuar kaskad üzerindeki birçok adımda etkili antiinflamatuar ilaçlardan biridir. Günlük pratiğimizde, lokal anesteziklerin kullanıldığı tedavilerden biri nöral terapidir. Nöral terapi, inflamatuar hastalıklar, ağrı ve fonksiyon bozukluklarının teşhis ve tedavisi amacıyla vücudun belirli bölgelerine, özel enjeksiyon tekniklerinin uygulandığı (lokal, segmental, ganglion ve bozucu alan enjeksiyonları), bir tedavi yöntemidir. Nöral terapide kullanılan lokal anestezik uygulamalarıyla otonom sinir sistemi tarafından iletilen anormal uyarılar önlenir, hücreler arası bilgi alışverişi kontrol edilir ve böylece otonom sinir sisteminin regülasyonu sağlanmış olur. Aynı zamanda nöral terapide, uzun yıllardır güvenle kullanılan lokal anesteziklerin antiviral ve antiinflamatuar etkileri çeşitli çalışmalarda gösterilmiştir. Lokal anesteziklerin, antiinflamatuar mediyatörlerin sentez ve salınımını etkileyerek, antiinflamatuar etkiyi, lizozim ile serbest radikallerin salınımı ve membran ATP az inhibisyonuyla antiviral etkiyi gerçekleştirdiği düşünülmektedir. Bu derlemede lokal anesteziklerin ve nöral tedavinin, virüs enfeksiyonları üzerindeki etkilerinin literatür ışığında tartışılması ve koronavirüs enfeksiyonu üzerindeki olası yararlı etkilerinin değerlendirilmesi amaçlanmıştır.

Anahtar Kelimeler: Nöral terapi; lokal anestezik; koronavirüs; COVID-19

One of the most common clinical symptoms of virus infections is the common cold. The common cold is a short-term disease, the main symptoms of which include the upper respiratory tract with predominant nasal symptoms. Human coronaviruses are the second most common cause of the common cold.

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Peer review under responsibility of Journal of Traditional Medical Complementary Therapies.

Received: 03 Nov 2020 ***Accepted:*** 26 Nov 2020 ***Available online:*** 22 Jan 2021

They make up 15-30% of proven viral infections.[1] Coronaviruses (CoV) are enveloped RNA viruses that cause respiratory, enteric, hepatic and neurological diseases. Six CoV species are known to cause human disease. Four viruses-229E, OC43, NL63, and HKU1-are common and typically cause common cold symptoms in individuals with a weakened immune system. The other two strains-severe acute respiratory syndrome CoV and Middle East respiratory syndrome CoV-are of zoonotic origin.[2]

Coronavirus disease-19 (COVID-19) is a viral disease that can seriously damage the respiratory system, including the lung, in humans and animals. When COVID-19 infects the upper and lower respiratory tract, it can cause mild or highly acute respiratory syndrome, resulting in the release of pro-inflammatory cytokines, including interleukin (IL)-1β and IL-6. Binding of COVID-19 to toll-like receptor results in the production of IL-1β, which causes lung inflammation, fever and fibrosis.[3] It may cause bronchitis, pneumonia and fibrosis following severe infection of the lower respiratory tract. The severity of the disease depends on the effectiveness of the immune system; if the immune system is weak, it cannot stop the infection and its symptoms. No drug has been found to treat COVID-19 flu so far. Medicines used in treatment are those for the virus-induced side effects such as inflammation and pulmonary fibrosis, which are considered the primary causes of death. The suppression of the pro-inflammatory IL-1 family members and of IL-6 have been shown to have a therapeutic effect in many inflammatory diseases, including viral infections.[3] Therefore, treatments used against inflammation should be considered.[4]

Local anesthetics (LAs) are medications that have been used safely for a long time.[5] The method of treatment used to diagnose and treat inflammatory diseases, pain and dysfunctions in the body and which involves the injection of LAs into scars, acupuncture points, tendon and ligament insertions, peripheral nerves, autonomic ganglia, trigger points, and other tissues is defined as neural therapy (NT).[5-7]

NT was discovered by Ferdinand and Walter Huneke in 1926 and their work was published under the name of 'Unknown distant effects of analgesics' in 1928.[6,8] In NT, procaine and lidocaine are the most commonly used local anesthetics.[6] In this review, we tried to review the possible beneficial effects of neural therapy on the treatment of viral infections. Possible efficacy of LAs in viral infection treatments can be grouped under several headings.

ANTIVIRAL EFFECTS OF LOCAL ANESTHETICS

In a study investigating the effects of some LAs (dibucaine, tetracaine, cocaine, lidocaine, and procaine) on bovine kidney cell fusion caused by the herpes simplex virus, all local anesthetic agents were reported to significantly inhibit cell fusion when used in physiologically appropriate concentrations. The authors suggested that local anesthetics inhibit cell fusion by invading regions within the plasma membrane that must be empty for virus-induced membrane fusion to occur.[9]

In a double-blind, placebo-controlled cross-study in patients diagnosed with herpes simplex virus (HSV), the LAs used were shown to reduce HSV infectivity. This effect was thought to be due to the interaction of LAs with the physicochemical properties of the virus envelope or inhibition of viral replication.[10]

Antiviral effects of LAs are thought to occur with release of free radicals by lysozyme and inhibition of membrane ATP-ase.[11-13] Ricker was of the opinion that, in a neurally controlled creature, bacteria would never be the primary cause of a disease unless they were disturbed, and that it depends on the environmental conditions and culture environment that bacteria can be effective and ensure their pathogenic reproduction. Ricker's opinions were supported by experimental studies that showed that viruses could bind to cells, but could only penetrate when the electric potential of cells fell to a certain point. While psychological and physical trauma changes this electrical potential to support pathogens, the use of procaine can restore cell potential to normal, thereby neutralizing the viruses in its environment.[14]

In addition, antibacterial and antifungal effects of LAs have been shown in many studies.[15] It has been thought that LAs may be associated with the interaction of macromolecules on the bacterial wall or on the

cellular surface of bacteria.[10] Therefore, LAs can also be useful in secondary bacterial and fungal infections in viral infection treatments.

ANTI-INFLAMMATORY ACTIVITY OF LOCAL ANESTHESICS

Inflammation is a local protective response to vascularized tissues against all types of damage. Excessive inflammatory response can cause tissue destruction and dysfunction.[10,16] The anti-inflammatory effects of local anesthetics have been shown in many studies.[10,17,18] LAs are effective in many steps on the inflammatory cascade. By activating the integrins and interacting with leukocyte adhesion molecules 1, they inhibit leukocyte adhesion to the endothelium, and also reduce the motility of leukocytes depending on the dose.[17-19] It has been observed in studies that local anesthetics decrease the phagocytic activities of granulocytes.[20] They achieve these effects by disrupting leukocyte surface receptor expression and inhibiting the actomyosin filament activity.[21] LAs also reduce the release of arachidonic acid from membrane phospholipids.[22] They have inhibitory effects on prostaglandin biosynthesis.[23] They reduce thromboxane B2 release.[24] They increase the inhibition of LTB4 released from activated granulocytes and monocytes.[25] They are thought to decrease histamine release in mast cells.[26] LAs were shown to inhibit the metabolic activity of leukocytes, superoxide anion formation, and free radicals.[27] LAs are also effective on cytokine release. Lidocaine and bupivacaine were shown to inhibit IL-1 released from activated monocytes.[28] In another study, lidocaine was observed to reduce TNF-alpha.[29] LAs were also shown to reduce edema triggered by inflammation.[30,31] Neutrophils and their lysosomal enzymes, proteases and free radicals are very important in lung injuries. LAs have been investigated in lung injuries due to the aforementioned anti-inflammatory effects. In an animal study, pulmonary edema was observed to decrease with intravenous lidocaine administration in lung edema caused by *E. Coli* endotoxin.[32]

In a study investigating the release of inflammatory mediators after acute lung damage caused by hyperoxia, clinically relevant concentrations of intravenous lidocaine infusion significantly reduced the release of cytokines (IL-1β, TNF-α) from the injured lung, with reduced flow and metabolic activation of neutrophils.[10]

In a study investigating lung damage revealed with HCl in rabbits, a reduction in lung tissue damage and pulmonary edema was observed morphologically and histologically in the lidocaine-treated group, and this was attributed to the inhibition of the sequestration and activation of neutrophils by lidocaine.[33]

In mice, the administration of lidocaine, which prevents neutrophil adhesion to endothelial cells in acute lung injury caused by bleomycin, was able to inhibit exacerbation of pulmonary lung injury caused by granulocyte colony, lung fibrosis and other morphological changes.[34]

In a study in which ischemic-reperfusion injury was created in the lungs of mice with toxic oxygen metabolites, the administration of lidocaine at a dose of 5 mg/kg reduced significantly pulmonary edema, pulmonary artery pressure and peak airway pressure. As a result, it was concluded that lidocaine is effective in preventing ischemic reperfusion injury in isolated, perfused rat lung.[35]

EFFECTS OF LOCAL ANESTHESIA ON CIRCULATION

Neural treatment is a regulative therapy for normalizing dysfunctional autonomic nervous system. This form of treatment uses regulatory mechanisms and plastic properties of the nervous system. It has positive impact on both the organization of the nervous system and tissue perfusion.[36] NT is used in the treatment of Sudeck's atrophy, Raynaud's disease and Buerger's disease caused by vasoconstriction, ischemia and tissue damage resulting from excessive sympathetic activity.[5-38]

In a study in mice, lidocaine was shown to protect against myocardial injury associated with persistent regional ischemia, reducing infarct size by 27%.[39] With these features, it was thought to be effective in tissue ischemia caused by infection.

HOW CAN LOCAL ANESTHETICS BE ADMINISTERED IN VIRAL INFECTIONS?

The use of LAs as nasal spray can be effective at the onset of the common cold. To stop the disease at the

initial stage with all the accompanying symptoms, 1 mL of procaine or lidocaine is administered into the antecubital fossa via intravenous route.[40] Before the needle is completely withdrawn, 0.5 mL should be injected out of the vein.[41]

Procaine has been reported to have an important therapeutic effect on nervous, cardiovascular, locomotor, cutaneous and gastrointestinal diseases of the elderly. It has also been shown that when procaine is combined with an alkaline substance, its anti-inflammatory effect is particularly high. Procaine infusion with alkaline additive is known as Procaine-Base-Infusion therapy. If there is no information about LAs allergy before infusion, the patient should be tested with a drop of 1% procaine into conjunctiva. If the burning sensation persists for a few minutes, treatment should not be administered. It is recommended to start with a dose of 50-100 mg of procaine-HCl and 20 mL of sodium hydrogen carbonate (8.4%) diluted in a 250 to 500 mL carrier solution. Infusion should take about 45-60 minutes. With increments of 50 mg procaine-HCl and 10 mL sodium bicarbonate (8.4%), Procaine-Base-Infusion should be administered until the desired therapeutic effect is achieved. The maximum dose of procaine-HCl for a person with normal weight is 300 mg. It should be used within two hours. After the treatment, the patient should be kept under observation for 30 minutes and it should be advised not to drive until 1 hour after the treatment.[42]

In NT, C3-C4 and T3-T5 segmental intracutaneous (quaddle) LAs injection is administered bilaterally in the basic treatment of lung diseases. If the patient's complaints increase, the treatment area is extended to bilateral C3-C8 and T1-T9.[43] To strengthen immunity, the segment of the spleen is treated as an organ. For this, intracutaneous (quaddle) LA injection is administered to the anterior and posterior reflection areas of the T8-T9-T10-T11 dermatomes on the left side. To increase the efficiency of the treatment, celiac ganglion injection can be administered on the left side.[43,44]

In cases where segmental therapy is ineffective, it is necessary to look for disruptive areas. Disruptive areas are those zones that appear after physical and mental traumas, and cause illness in the body as a result of the incomplete biological recovery. Disruptive areas can disrupt the body's healthy healing mechanisms by creating a dysfunction in the autonomic nervous system. LA injections into these areas can eliminate the barriers to healing.[36]

Any skin changes, including all sorts of scars, dental foci, intestinal dysbiosis, piercings, tattoos, and burns, can be disruptive areas.[6]

In resistant diseases that occur in the lung, such as pneumonia, we must first focus on the mouth, nose and throat region. Here, teeth, sinuses and tonsils that may have pathogenic effects should be investigated.[40]

The COVID-19 report by World Health Organization, dated Sept. 16, 2020, reported the number of diseases in the world as 29,155,581 and the number of deaths as 926,544.[45] In order to cope with the human CoV pandemic, which is seen in almost every country in the world, it is only recommended that individuals be isolated from each other and stay at home in quarantine to limit viral transmission.[4] No medication or vaccine has yet been approved for its treatment. It is reported that these treatments require months or years to develop.[46]

In conclusion, due to the prediction that the CoV pandemic will continue for a long time, we believe that NT, administered with LAs that have been shown to be effective on viruses and inflammation through long years of studies, can be administered together with other treatments as a supportive treatment in the COVID-19 pandemic.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Turgay Altınbilek, Rabia Terzi, Elif Kaya, Sadiye Murat;* ***Design:*** *Turgay Altınbilek, Rabia Terzi, Sadiye Murat;* ***Control/Supervision:*** *Elif Kaya, Sadiye Murat;* ***Data Collection and/or Processing:*** *Turgay Altınbilek, Rabia Terzi, Elif Kaya, Sadiye Murat;* ***Analysis and/or Interpretation:*** *Turgay Altınbilek, Rabia Terzi;* ***Literature Review:*** *Rabia Terzi, Elif Kaya, Sadiye Murat;* ***Writing the Article:*** *Turgay Altınbilek, Rabia Terzi, Elif Kaya, Sadiye Murat;* ***Critical Review:*** *Turgay Altınbilek, Rabia Terzi, Elif Kaya, Sadiye Murat;* ***References and Fundings:*** *Turgay Altınbilek, Rabia Terzi, Elif Kaya, Sadiye Murat;* ***Materials:*** *Turgay Altınbilek, Rabia Terzi, Elif Kaya, Sadiye Murat.*

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