Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2016;5:3:249-256.

Smoking and Chronic Pain: Compound Interactions

Ridam Jain[1*] Tanmay Sharma[2] Arpit Viradiya[3] Mukundi Dhaduk[4]

[1]Reader, Department of Orthodontics, Darshan Dental College and Hospital, Udaipur, Rajasthan, India.
[2]Reader, Department of Orthodontics, Azamgarh Dental College & Hospital, Uttar Pradesh, India.
[3]Post Graduate Student, Department of Conservative Dentistry, Pacific Dental College and Hospital, Udaipur, Rajasthan, India.
[4]Post Graduate Student, Department of Orthodontics, Pacific Dental College and Hospital, Udaipur, Rajasthan, India.

ABSTRACT

Background: Smoking is a major public health problem. Cigarette smoking acts as a nicotine delivery in humans, has found to produce profound changes in physiological architecture. Smoking's as well as chronic pain are one of the major challenging health concerns faced in day to day life. During smoking nicotine is quickly absorbed into the blood stream within a time gap of 30 seconds it reaches the brain. It stimulates the brain to release various chemicals namely epinephrine which will give a pleasurable euphoric effect. It is a proven fact that smoking of tobacco will cause the production of Rheumatoid factors or anti-cyclic citrullinated peptide autoantibodies which is a risk factor for the development of Rheumatoid arthritis. There is a positive relation between smoking and depression and it has been seen smokers use more number of cigarettes when depressed and smoking also caused the individual who is depressed more prone to pain than a normal smoker. Quitting of smoking is quite difficult because of unpleasant withdrawal syndrome that consists of frustration, depression, anxiety, reduced heart rate, increased weight, depressed mood, difficulty in concentration. Because of all these withdrawal symptoms individuals who try to quit start up again very soon. Smoking is a health hazard, this is a well-known fact and the noxious effects are multiple so in management of pain in theseindividual's, necessary steps has to be put forward in order to quit the habit. Cognitive behavioural therapy or antidepressant therapy in the management of pain of depressed patients who are smokers has shown good results in a rehabilitation centre on the course of the management of pain.

Keywords: Chronic pain, Cigarette, Rheumatoid arthritis, Smoking.

INTRODUCTION

Smoking is a major public health problem. Cigarette smoking acts as a nicotine delivery in humans, has found to produce profound changes in physiological architecture. Mortality with the habit of smoking is high and the death happens as a result of cancers, breathing problems, strokes etc and it even causes disabilities, pain and will make them prone to many diseases. Pain is one thing which significantly interferes with the quality of life as pain affects the physical as well as mental status of an individual.[1]One of the major health problem is the musculoskeletal complaints. It seems to show increasing in the prevalence rate and possess an economic burden to the society.[2] this review article will be contenting pain perception both acute and chronic pain in smoking. And the mechanism to explain the association of smoking and pain. Smokings as well as chronic pain are one of the major challenging health concerns faced in day to day life. Before reviewing how acute and chronic exposure to nicotine of cigarette smoke causes acute and chronic painful conditions, one should know the relevant pharmacology of nicotine and other ligand s at nAChR. This is important to know the mechianics as well as for identifying the potential targets for the management of smoking

Received: Mar. 11, 2016: **Accepted:** May. 7, 2016
***Correspondence Dr. Ridam Jain.**
Department of Orthodontics, Darshan Dental College and Hospital, Udaipur, Rajasthan, India.
Email: drpiyushpujara@gmail.com

pISSN 2278-0076
eISSN 2321-9270

associated pain as well as important in the development of drugs.[1]

Pharmacology of Nicotine Acetylcholine Receptors

Two types of nicotine receptors are present in human body Nm and Nn. Nm are present in skeletal muscle and Nn are present in ganglionic cell, adrenal medullary cell and spinal cord. Nicotine affects through nAChR, which is a pentameric complex of transmembrane protein that has a central pore permeable to sodium, calcium, and potassium ions.[3] in muscle type nAChR structure is different for adult and foetus. For adult it is (α1)2β1δε and for foetus is (α1)2β1δγ.[4] Neuronal nAChR have different combinations of α(α2-α10) and for nonα it is β2 – β4.[5] Ach bind at interface between α subunit and neighbouring subunit and thus binding with nAChRs will depend on their subunit composition.

These nAChRs are widely distributed in central and peripheral nervous system. Homomeric receptors α7 and hetromeric α4β2 are mainly present in central nervous system.3This α4β2 receptor has two binding sites for agonist and competitive antagonist and α7 nAChRs have 5 binding sites.[3,6] In dorsal horn of spinal cord, thalamus, and other brain region α4β2 receptors are present that are associated with nociceptive transmission and modulation.[7,8] Similarly in dorsal root ganglia, leukocyte, vestibular and cochlear mechanosensory hair cell and other tissue α9α10 nAChR is present.

Direct excitatory neuronal effects are produced by activation of post synaptic nAChRs via cationic channels. Activation of presynaptic nAChR causes release of neurotransmitters like dopamine, glutamate, serotonin, histamine and norepinephrine. Thus effect of nicotine and other nAChR ligands is produced by released neurotransmitter.3,5 Multiple ligands and modulators such as neurosteroid, local anaesthetic, phencyclidine and MK801 are for neuronal nAChRs.[9] In relevant doses inhibitors for α4β2 and α3β4 are volatile anaesthetic and ketamine. Complex pharmacological action is because of nAChR subunits that has varying selectivity. Along with this kinetic of nAChR channel opening also varies. On high concentration and short exposure of ACh there is fast opening of nAChRs while prolonged and chronic exposure leads to closed and desensitized state.[3] Change in receptor number or function can also occur during prolonged exposure. Animal experiments have shown 2 fold increase in nAChR due to prolonged exposure of low level nicotine that similar to what is seen in chronic smokers.[10,11] When compared in smokers and nonsmokers positron emission tomography have shown greater densities of high affinity AChRs in brain. These aspects of nAChR pharmacology is important for understanding the mechanics as well as for definitive management measures and drug therapy.[12]

An overview of the literatures

Tobacco smoking has got dependence and the reason behind this is chemical agent in the cigarette known as nicotine. While smoking numerous chemical agents are produced but the addictive agent is nicotine alone. During smoking nicotine is quickly absorbed into the blood stream within a time gap of 30 seconds it reaches the brain. It stimulates the brain to release various chemicals namely epinephrine which will give a pleasurable euphoric effect.[13] this effect is short lived and fades away and crave for the pleasure that has been felt remains and this explains the addiction of cigarette smoking. It should be kept in mind that many of the studies regarding the chronic pain and smoking found that smoking rates are higher than the population rates and moreover researchers are categorizing the patients as smokers and non-smokers in pain related complaints.[14]

Brage and Bjerkedal were one among the first researchers who did a study on smoking and relation to pain in Norway. They conducted a study on 6681 smokers and reported the subjects to be suffering from musculoskeletal pain, especially in the neck, back and upper limbs.[15]Population based studies showed current smokers as well as former heavy smokers reported with a much higher pain intensity than nonsmokers.[14] Many studies have been conducted in US, survey has found out 1 in 5 Americans smoke and around 20.6% of American adult population is current smokers and various pain studies have quoted smoking rates to be high in the group.[16]

It is a proven fact that smoking of tobacco will cause the production of Rheumatoid factors or anti-cyclic citrullinated peptide autoantibodies (anti-CCP Abs) which is a risk factor for the development of Rheumatoid arthritis.[17] But looking into the literatures and studies conducted world-wide gave results which is debatable and the cause for the uncertainty is lack of clear cut causal mechanism to prove the relation.[18]Enumerable hypothesis has been stated to discover the relation of smoking and chronic pain but it is a challenging to prove and disprove these hypothesis because the data's which exist are cross sectional and also there are many factors which will precipitate the pain. So it is challenging to point out the causal relation until and unless it is particularly strong.[14] Tobacco is used in various forms other than smoking like chewable and snuff and no relation with pain was found in individuals with the usage of these forms of tobacco but relation is found in individuals who were past smokers but study failed to state the time period the users has given up the habit.[19] Considering confounding factors such as socio-economic status, psychological factors, and as well as the life style and nature of their occupation do play a role with tobacco smoking. Among smokers those having their occupation which will have much standing and lifting heavy loads was predicted to have back pain within four years whereas non-smokers were not predictable and it came out to be true for other confounding factors as well. It was also well proven that individuals with low educational status were more likely to present with the complaint of low back pain.[18,20,21,22]

A population based cohort study conducted by Synnøve Kvalheim et al showed a 20% increased risk for chronic musculoskeletal disorders. This was especially evident in those individuals who are more than 50 years of age. The study had sufficient sample size to be statistically sound. They suggested that smoking as it is a modifiable risk factor in musculoskeletal aid has to consider in the health intervention programs. Although they pointed out the reason for age dependant smoking effect on the musculoskeletal pain is not obvious. Many epidemiological studies have shown the positive relation between smoking and chronic musculoskeletal pain but only few studies are conducted taking the age as a factor and showing the interaction.[2] However in a meta-analysis done among young individuals showed a stronger association between smoking and chronic low back pain. This study stated that adolescent are more vulnerable to the effects of smoking than the adults. Explanation given was chronic musculoskeletal pain is less tolerated in young individuals and smoking as it contains nicotine having antinocioceptive property will act as a pain modulator thereby relieving the individual out of stress. In these individuals smoking will be continued due to the stress relieving effect and they rarely give up the habit.[23,24]

In addition to the relation of smoking and pain studies conducted has proved the smokers in addition to the increased pain intensity have also reported with more number of painful sites.[4] There is a positive relation between smoking and depression and it has been seen smokers use more number of cigarettes when depressed and smoking also caused the individual who is depressed more prone to pain than a normal smoker.[25]A study has conducted taking into account the multivariate association with smoking depression as well as pain. This study showed a positive relation with smoking and pain but this association weakened when controlling for depression. A study conducted among adolescent smokers found out that daily smoking affected multiple somatic and psychological healths. Psychological health is a known factor for the musculoskeletal disorders so this study says that smoking indirectly through its effect on the psychological health status results in chronic musculoskeletal painful condition.[26,27,28,29]

This throws a light into the interlinking factor depression. Testimonials of smokers says smoking elevates their mood and they have been considered as a selfmedication by them for depression.4 The study data draws us to the conclusion that in outpatient clinic patients presenting with chronic pain were high and the smoking rates were too. Patients who smoked presented with the most severe painful condition. Taking depression as a major factor helps up to draw a better conclusion in the relation of pain and smoking. On over viewing the literatures it has been found that cigarette smoking relation to pain has no statistical difference in the number of cigarette smoked per day and thereby this study signifies that for prevention of musculoskeletal pain one should

stop smoking and reducing the number of cigarettes per day will not have any effect.[21] Cigarette smoking if habitual because of the cognitive effect of the nicotine in the tobacco smoke. It has been documented in literatures that longer the duration of the quit of smoking less will be the severity of pain but more studies has to be made to prove dis statement. A result of a cohort study conducted concluded that students aged 14 years approximately who smoked has a high risk of low back pain.

In a longitudinal study conducted among the blue collar workers in Finland came up with a conclusion that smoking is a predictive factor for musculoskeletal pain and also cessation of smoking lead to musculoskeletal symptoms.[21] Smoking does not stands only for chronic back pain but also in shoulders, hands, neck, elbows and knees and the study was focused on the oro-facial pain relation to smoking, study stated that there is an increase incidence in TMJ pain in smokers than other individuals. The physiology behind this is the nicotine gets accumulated in the body during the day hours and decreases once the individual rests so the action of nicotine in the acetyl choline receptors can enhance glutamatergic synaptic transmission which will results in increased dopamine release and this follows increased nicotine followed by increased dopamine release and this relates to the increased oromotor activity.[30]Looking into the clinical aspect it was found that after 3rd molar surgery individuals who smoked more than 10 cigarettes a day required higher dosage of the pain killers used when compared with nonsmokers.

Although controversial smoking is said to be a major factor in risk of getting macrovascular diseases in diabetes mellitus patients and is also associated with macroproteinuric neuropathy in insulin dependent diabetes mellitus individuals.[31] It has been also reported in literature that tobacco use is associated with an increased incidence of tooth ache as well as other oral soft tissue pain and the impact of pain has reduced after the cessation of the tobacco habits. Scot et al did a comparative study on smoking and low back pain in adolescent idiopathic scoliosis (AIS) and a control group, he found a closer association with the AIS group. Eriksen et al did a study and result was, the odds ratio was high in heavy physical workers who are smokers than non-smokers. These studies draw us to a conclusion that smoking acts as a modifying factor in people having damaged spine as well as people with heavy workloads which leads them to increased damage and thereby acts in aggravating the pain.[20]

An association of smoking and chronic pain and its relation to the poor socioeconomic status as well as psychosocial status has been described. It is seen that people of low socioeconomic status as well as people affected with heir psychosocial status like low education, divorced individual, unemployment and so on. It is found that these individuals are not able to cope up with their pain symptom that in turn contributes to chronic pain. A reasonable question comes into our mind whether a former smoker will have the same effect of a current smoker or will he have the benefit of a non-smoker. Epidemiological studies conducted have shown differences between the former smoker and a non-smoker in relation to pain and it was found that former smokers reported to have comparatively more pain severity than non-smokers.[32] But many other studies reported that the former smokers reported with same pain intensity and differences between them were negligible.[14] This knowledge should be kept in mind as a prime factor during the management of pain in the smoking population and necessary measures should be taken to make the individual to quit the habit as it may have positive impact on outcomes. Specific outcome results cannot be drawn because little attention for the habit cessation has been made in the management of chronic pain in smoking population in outpatient basis. Point conclusions cannot be drawn because of ineffective measures and reported low cessation rates during the management.[33, 34]More experimental studies are needed to draw valuable data's and clear the path for the management measures.

Possible pathology behind the relation

Nicotine is having analgesic property but it is found that chronic smokers associated with chronic pain this fact seems surprising and the possible reasons for this relation is described below. In a normal individual the psychological stress is anticipated by the sympathetic system and hypothalamic – pituitary – adrenal (HPA System)

axis but in smokers this HPA system is suppressed. Smoking causes degenerative changes in the body like osteoporosis lumbar disc diseases and also impairs bone healing these factors make the smokers prone to injury as well as compromised healing and will lead to chronic pain. The tissues get hypoxic due to the impaired oxygen perfusion due to the increased sympathetic outflow as well as increased carboxyheamoglobin levels.[4]

Psychological factors has also shown a positive relation, smokers are found to have high rates of psychological variation like depression and anxiety than non-smokers and these mood variation is associated with more chronic pain. The exact relation of smoking, depression and chronic pain is complex and yet not understood completely. But it has been said in literatures that pain and depression are thought to hare common neurophysiological pathway so hence depressed smokers can experience more pain due to this interaction.[14]

Smoking leads to reduced perfusion to the spine tissue thereby causing tissue anoxia and malnutrition of the spinal tissues making it more prone to any mechanical injury during stress. So any stress in physical form will induce more injury to the tissues as compared to normal tissues. Reason behind this is the catecholamine release and other toxic chemicals products produced during smoking like cadmium, nicotine, cyanide and carbon monoxide will reduce blood flow.[18,34]

Increase in the viscosity of the blood due to the induced erythropoiesis by increased carboxy-heamoglobin and long term inhibition of prostaglandin E2 production by nicotine. Patients taking opioid analgesics for chronic pain, smokers were found to take high doses than non-smokers and yet pain was not relieved. The reason behind this is the polycyclic aromatic hydrocarbons in the tobacco smoke induces P450 enzymes involved in morphine metabolism thereby reducing the bio-availability of the drug. Nicotine although having an antinocioceptive action once deprived will result in easy perception of pain and reduced tolerance to pain. Nicotine can increase the concentration of calcium ions which will result in muscle contractions so it will lead to fatigue and pain.[15]

Smoking causes reduction in the bone density and also reduction of blood supply to the vertebrae which makes prone to injury as well as pain and the mechanism behind this is carboxyl haemoglobin formation, vasoconstriction, arthrosclerosis and haematological impairment.[18]

SMOKING CESSATION APPROACHES

Quitting of smoking is quite difficult because of unpleasant withdrawal syndrome that consists of frustration, depression, anxiety, reduced heart rate, increased weight, depressed mood, difficulty in concentration. Because of all these withdrawal symptoms individuals who try to quit start up again very soon.[35] A clinical practice guideline for treating tobacco use and dependence was released by US public health services in 2000. Guidelines in briefed about techniques for quitting cigarette smoking. They found that for people, who are willing to quit the habit, counseling and medications are helpful and this approach has proved efficient results.[36]

Counseling

This can be in form of brief intervention when a doctor gives an advice for few minutes regarding quit of habit. It can be group, individual or telephone counseling. A relatively newer form of telephone counselling called proactive telephone calls is found to be effective.

Problem solving approach is also found to be effective in many smokers. Under this approach individual are asked about when they mostly wants to smoke and then work is planned out at that time this would help to distract there urge for smoking. Support caring attitude and encouragement by family members and friends (extratreatment social support) and from healthcare providers (intratreatment social support)also help in quitting the habit successfully.[35] 5 Medicines are approved by US food and drug administration FDA for quitting the habit. These include 4 nicotine replacement therapy and 1 is non-nicotine agent. Replacement therapy includes gum, inhaler, patch and nasal spray. This therapy not only relieves withdrawal symptoms and urge to smoke it also decreases the smoker's exposure to carbon monoxide tar and other carcinogen. Non-nicotinic agent includes bupropion.[36]

Table 1: FDA approved medication for smoking cessation (smoke cessation)

Name	Forms	Dosage	Length of use	Precautions/ Contraindication	Side Effects
Bupropion, sustainedrelease	Zyban prescription only)	150 mg in morning for 3 days, then 150 mg twice a day	Begin 1–2 weeks before quit date, then 7–12 weeks	Seizure, eating disorder	Insomnia, dry mouth
Nicotine gum	Nicorette, Nicorette DS, Nicorette Mint, Nicorette Orange (OTC only)	Up to 24 pieces/day; ,25 cigs/day 3 2 mg; $25 cigs/day 3 4 mg	Up to 12 weeks		Sore mouth, dyspepsia
Nicotine inhaler	Nicotrol Inhaler (prescription only)	6–16 cartridges/da y	Up to 6 month s		Mouth/throat irritation
Nicotine nasal spray	Nicotrol NS (prescription only)	8–40 doses/day	3–6 month s	Dependency	Nasal irritation
Nicotine patch	Nicoderm CQ (OTC only), generic/hous e brand patches (OTC and prescription) Nicotrol (OTC only)	21 mg/24 h; 14 mg/24 h; 7 mg/24 h; 15 mg/16 h	4 weeks; then 2 weeks; then 2 weeks 8 weeks		Local skin reaction

OTC indicates over the counter. Zyban, Nicorette, and Nicoderm are products of Glaxo SmithKline; Nicotrol is a product of Pharmacia, Inc. Since smoking is highly addictive in nature patient should be counselled again and again regardless of many unsuccessful attempts. Repeated attempts should be made not only from individual but also family members and society.[36]

CONCLUSION

As we all know smoking is an environmental risk factor and has many deleterious effects on human body. A study conducted in England about smoking concluded that smoking causes disadvantage to the individual in multiple dimension i.e the physical, mental as well as social health. On-going through the literatures it has been found that in many studies regarding the relation of smoking to back pain showed no statistical differences regarding the number of cigarettes smoked per day as well as the frequency of smoking. The studies also failed to show the validity and difference if any, in the relation between smoking and pain when gender is taken into consideration as well as a clear cut pathogenesis is lacking to prove a strong relation so tobacco smoking always stays as an elusive factor but all the studies shows a positive relation too. This concludes that smoking acts like a confounding factor or a supporting factor which will lead soon to the pathology. More studies has to be conducted for the discovering the definitive explanation for the relation as well as more studies has to be conducted to throw light on the gender difference and effects as well as statistically sound studies to discover the frequency and duration of the habit and the relation. Smoking is a health hazard, this is a well-known fact and the noxious effects are multiple so in management of pain in theseindividual's,

necessary steps has to be put forward in order to quit the habit. Cognitive behavioural therapy or antidepressant therapy in the management of pain of depressed patients who are smokers has shown good results in a rehabilitation centre on the course of the management of pain. This approach has proved effective as well as some classes of anti-depressants have analgesic property too aiding in effective pain relief to the individuals. Smoking cessation too should be considered as the prime goal in management of these patients and they will experience the dramatic benefits of stopping the habit in a long term health basis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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