

DE-ADDICTION POTENTIAL OF CLOVE (*EUGENIA CARYOPHYLLATA* LINN.) IN OPIATE ADDICTION IN SICKLE CELL DISEASE

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ABSTRACT

Pain due to vaso-occlusive crisis is a universal human experience for sickle cell disease, as it defines the symptom of SCD. Objective measures of the presence and severity are lacking in the pain management which is a challenging task. Acute and chronic pain in SCD shows the pervasive and unfounded fear of drug addiction and drug seeking behaviours. Over 3000 years, magical drugs of opiates have been the main stay of pain relief. Because of relapse of severe pain episodes, patients often get into vicious circle of addiction in SCD, have no choice except resorting to same opiates for pain relief. The excellence of medicinal plants with potent analgesic activity were

detailed decades ago, Clove, one such herb which contains volatile oils like Phyto cannabinoids and vanilloids will aid in relieving the pain in SCD. Eugenol interacts with vanilloids receptors in order to produce analgesia. Clove facilitates the de addiction of opiates. Whole clove can be chewed when craving is overpowering. Thus, this article tries to emphasize the action of clove in pain management of SCD which may prevent opiate addiction.

KEYWORDS: Clove (*Eugenia caryophyllata*), De addiction, Sickle cell disease, Opiate addiction.

INTRODUCTION

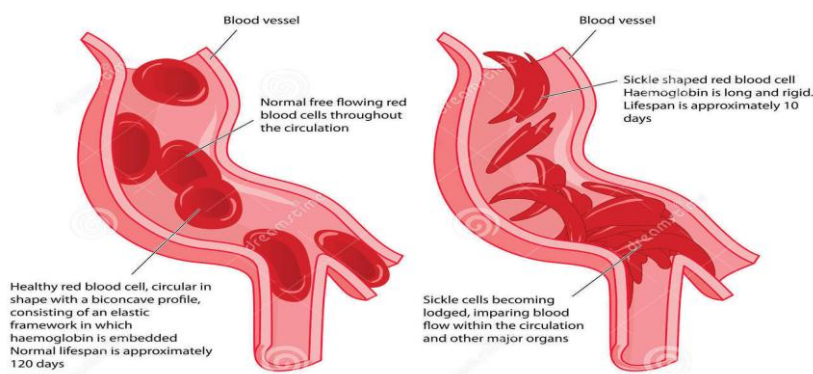
Sickle cell disease (SCD) affects millions of people worldwide and the disease is on the rise. Pain is a defining symptom of SCD that can begin in infancy and increase in severity throughout life.^[1] 70% hospitalization in emergency department occurs due to pain.^[2] The treatment of pain in SCD depends on whether the pain is acute, chronic or a mixture of the two.^[3] It is well recognized that objective measures of the presence and severity of pain is lacking.^[4] Opioids are the mainstay in the treatment of moderate to severe pain in SCD. They attach to receptors in the brain and suppress the pain perception.^[5] The lifelong progressive nature of pain in SCD necessitates chronic opioid use resulting in suboptimal analgesia and contributing to poor quality of life.^[6] As opiates have significant addictive potential and careless use of the drug can result in side-effects. Because of relapse of severe pain episode patients often get into vicious circle of addiction in SCD and they don't have choice except resorting to same opiates for pain relief.

Therefore, management of pain in SCD is quite challenging task so it must involve many other treatment modalities apart from opiates. So, present review article is an attempt to throw light on clove which has analgesic activity and may be a potential substitute to combat addiction.

AIM AND OBJECTIVES

1. To review the pain and opiate addiction in Sickle cell disease
2. To analyse the analgesic activity of Clove in SCD and evaluate the potential of Clove in de addiction of opiates.

Pain in Sickle cell disease



Sickle cell disease belongs to a family of disease known as hemoglobinopathies and is the most common genetic disease.^[7] It was first discovered in the United States in 1910. Biochemically, SCD occurs due to a non-conservative substitution of a polar glutamate (Glu) by a non-polar valine (Val) in an invariant region, the sixth position of Hb- β chain subunit.^[8,9,10] It is an autosomal recessive disorder containing 2 abnormal copies of the gene coding for the haemoglobin β chain.^[4] Replacement of this single non-polar amino acid 'Valine' results in a biochemical difference that leads to formation of a sticky patch on the surface of the β -chains. The sticky patch is observed on both the oxygenated (R- form) and deoxygenated (T- form) of HbS. This distorts folding and binding patterns of the Hb molecule, due to altered properties. Other known mechanism of polymerization of Hb in SCD involves nucleation, which is due to the aggregation of HbS molecules. At low oxygen level (hypoxia), deoxyhaemoglobin S polymerizes inside the red blood cells. This forms a network of polymers that stiffen and distort cells with rigid, misshapen erythrocytes.^[6]

Due to oxygen deprivation in the RBC, a critical aggregate of Hb polymer is formed that damages the cellular proteins, stopping the flow of blood in the narrow capillaries and leading to localized oxygen deprivation (anoxia).^[7,9,11] This polymerization is enhanced by the heterogeneous nature of the nucleus, where new polymers are continually formed on pre-existing polymer to form fourteen inter-wound helical strands of HbS. In each molecule, one of the two $\beta 6$ Valines of the $\alpha 2 \beta 2$ tetramer is involved in an intermolecular contact with its neighbour in the double strand.^[9,10] Formation of deoxy-HbS polymer makes the Hb insoluble, changes the biconcave structure of the red blood cells and eventually causes cell lysis, which leads to the various clinical features of SCD.^[7]

Sickle cell crisis occurs when sickle red blood cells block blood flow to any organ or tissue of the body leading to ischemic and hypoxic injury which manifests as severe and excruciating pain in the affected part of the body.⁸ Person with SCD frequently presents to emergency department with pain. Pain is a dominating feature of it. It is worse than postoperative pain and is as intense as terminal cancer pain.^[12,13]

Pain management and Opiate addiction

Pain is a hallmark of SCD and its treatment remains challenging. Opioids are the major family of analgesics that are commonly used for treating severe pain. Due to lack of objective measures of the presence and severity of pain, the pervasive and unfounded fear of drug addiction and seeking behaviour in acute and chronic pain of SCD is common.^[14,15,16]

When any opiate travels through the bloodstream to the brain, the chemicals attach to specialized proteins, called mu opioid receptors, on the surfaces of opiate-sensitive neurons (brain cells). The linkage of these chemicals with the receptors triggers the same biochemical brain processes that reward people with feelings of pleasure when they engage in activities that promote basic life functions. Opioids are prescribed therapeutically to relieve pain, but when opioids activate these reward processes in the absence of significant pain, they can motivate repeated use of the drug simply for pleasure.^[17]

One of the brain circuits that is activated by opioids is the mesolimbic (midbrain) reward system. This system generates signals in a part of the brain called the ventral tegmental area (VTA) that result in the release of the chemical dopamine (DA) in another part of the brain, the nucleus accumbent (NAc). This release of DA into the NAc causes feelings of pleasure. Other areas of the brain create a lasting record or memory that associates these good feelings with the circumstances and environment in which they occur. These memories, called conditioned associations, often lead to the craving for drugs.^[16]

Repeated exposure to opioid drugs induces the brain mechanisms of dependence, which leads to daily drug use to avert the unpleasant symptoms of drug withdrawal. Further prolonged use produces more long-lasting changes in the brain that may underlie the compulsive drug-seeking behavior and related adverse consequences that are the hallmarks of addiction. Recent scientific research has generated several models to explain how habitual drug use produces changes in the brain that may lead to drug addiction.^[18]

Stress and drug craving: The drug abuse patients are more vulnerable to stress than the general population is a clinical truism. In the research area, numerous studies have documented that physical stressors and psychological stressors can cause animals to reinstate drug use and that stressors can trigger drug craving in addicted humans. The likely explanation for these observations is that opioid raise levels of cortisol, a hormone that plays a primary role in stress responses; and cortisol in turn, raises the level of activity in the mesolimbic reward system. By these mechanisms, stress may contribute to the addict's desire to take drugs in the first place and to his or her subsequent compulsion to keep taking them.^[19]

The use of medicinal plants for treating various disease is probably the oldest method that mankind has used to cope with illness. Various medicinal plants demonstrated effect on SCD

symptoms. Renewed interest in plants for treating SCD was further stimulated, when Nicosan/ Niprisan (a product of extract form of four different plants) was reported to possess potent anti-sickling activity. Clinical trials have shown that the drug significantly reduces the number of clinical episodes in SCD patients.^[20] The group of phytochemicals and their synthetic analogues as components of *Eugeniacyrophyllata* and *Piper guineense*, may account for some of the useful effects of Niprisan in Sick cell crisis.^[21]

Clove



Clove, is a median size tree (8-12 m) native from the Maluku islands in east Indonesia.^[22]

Clove useful part is stem, Leaf and whole floral bud.

Common Name- Cloves, Caryophyllus, Clovos

Botanical Name- *Eugenia caryophyllata* Linn, *Syzguimaromaticum* Spreng.

Family- Myrtaceae

Sanskrit Name- *Badrasriya*, *Devakusuma*, *Devapuspa*, *Lavanga*.

Lavanga in Ayurveda is explained in many classical texts. The part of *Lavanga* that is used is the dried flower buds, leaves, stem. It has *Tikta*, *Katu rasa*, *Laghu*, *Snigdha* Guna, *Sita* Virya and *Katu* vipaka. It possesses qualities like *Kapha-Pitta-Asruknashak*, *Deepana*, *Pachana*, *Ruchya*, *Trishna*, *Chardi*, *Aadhaman*, *Shoolanashak*. And useful in diseases like *Kasa*, *Shwas*, *Hikka*.^[23]

Cloves come in 3 different forms, whole, ground and oil. All three forms have the same properties with differing degrees of potency. Oil has the highest potency and is best used diluted with carrier oil like almond oil. Whole cloves are medium potency the oils are still in them and they can be ground in a mortar and pestle for use. Ground cloves are the least potent, most of the oil has already been released.^[24,25,26]

Therapeutic use of Clove

1. Anesthetic- They are natural anesthetic and this is often used for medicines both topically and internally.^[27]
2. Powerful germicidal properties- Clove is used extensively in dental care for relieving toothache, sore gums and oral ulcers. Gargling with clove oil can also aid in sore throat conditions and bad breathe.^[28]
3. Antiseptic: Clove oil can be used to reduce infections, wounds, insect bites and stings. *et.al.*
4. Anti-fungal: Clove is also effective in reducing fungal infections such as athlete's foot. *et.al.*
5. Anti-Bacterial: An effective aid for food poisoning, clove oil effectively kills many forms of bacterial infections from contaminated foods.^[29]
6. Indigestion: Clove oil offers a powerful action against gas and bloating. It reduces gas pressure in the stomach, aiding in the proper elimination of food and toxins. It also relieves the discomfort of peptic ulcers. Effective for stomach related conditions including nausea, hiccups, motion sickness and vomiting. *et.al.*
7. Skin: Excellent aid for skin disorders, such as acne.^[30]
8. General Stress Reliever: Clove oil stimulates the circulatory system, clearing the mind and reducing mental exhaustion and fatigue. It has also been used to aid insomnia, memory loss, anxiety and depression. *et.al.*
9. Anti-Inflammatory: Clove oil clears the respiratory passages, acting as an expectorant for treating many upper-respiratory conditions including colds, eye stye, bronchitis, sinus conditions, cough and asthma. *et.al*
10. Blood Purifier: Not only purifies the blood, but also aids in stabilizing blood sugar levels, and may have benefits for diabetic individuals. *et.al*
11. General Immune System Booster: Clove's antiviral and cleansing properties purify the body, augmenting our resistance to disease. *et.al*
12. Premature Ejaculation: Some research has shown that clove may be useful as an aid for premature ejaculation. *et.al*
13. Prevention from toxic exposure: Studies show that clove oil can prevent toxicity related to exposure to environmental pollution.*et.al.*
14. Cancer Prevention: Preliminary studies suggest that clove oil may play a chemo preventive role, particularly in cases of lung, skin and digestive cancers.^[31, 32]
15. Cardiovascular Health: The active essential oil in clove, eugenol, has been shown to act as an effective platelet inhibitor, preventing blood clots.^[33]

Chemical compounds

Clove represents one of the major vegetable source of phenolic compounds as flavonoids, hydroxybenzoic acids, hydroxycinnamic acid and hydroxyphenylpropene. Eugenol is the main bioactive compound of clove, which is found in concentration ranging from 9381.70 to 14650 mg per 100 g of fresh plant material.^[34]

With regard to the phenolic acids, gallic acid is the compound found in higher concentration. However, other gallic acid derivatives as hydrolysable tannins are present in higher concentration.^[35] Other phenolic acids found in clove are the caffeic, ferulic, elagic and salicylic acids. Flavonoids as kaempferol, quercetin and its derivatives (glycosylated) are also found in clove in lower concentrations.

Concentrations upto 18% of essential oil can be found in the clove flower buds. Roughly 89% of the clove essential oil is eugenol and 5% to 15% is eugenol acetate and β -caryophyllene.^[36] Another important compound found in the essential oil of clove in other volatile compounds present in lower concentrations in clove essential oil are β -pinene, limonene, farnesyl, benzaldehyde, 2-heptanone and ethyl hexanoate.^[37]

Clove as an analgesic in SCD: Eugenol has a short hydrocarbon chain attached to the ring, which makes it much less water soluble than vanillin. Although it is practically insoluble in water, it freely mixes with fats and oils. Its fat solubility allows it to penetrate tissues and bind more tightly to lipid rich membrane bound vanilloid receptors. The tail gives eugenol a stronger odor than vanillin. Eugenol, has a numbing analgesic effect. It is supposed that the hydrocarbon tail in combination with the polar OH group on the ring allows eugenol to interact with vanilloid receptors in order to produce analgesia and other physiochemical effects.^[38]

β -Caryophyllene has been found to bind selectively to CB2 i.e. cannabinoid receptor expressed in the immune system, hematopoietic cells and peripheral nerve terminals where they function in pain control, and to exert significant cannabimimetic effects in mice. This implies that caryophyllene can relief pain in humans and be of benefit to SCD patients.^[39]

Clove in Aromatherapy: Clove essential oil is recognized as safe substance, and many studies reported its antimicrobial and antioxidant property. Clove essential oil can be used in aromatherapy.^[40]

Aromatherapy is use of essential oils from plants to support and balance the mind, body and spirit. It is used as a form of supportive care that may improve quality of life and reduce stress and anxiety. Most studies as well as clinically applied experience have indicated that various essential oils can help to relieve stress, anxiety, depression and other mood disorders. The mechanism of action of inhaled aromatherapy state with the absorption of volatile molecules through the nasal mucosa. Odor molecules are then transformed into chemical signals, which more towards the olfactory bulb and possibly other parts of limbic system, stimulate the brain to exert neurotransmitters thereby further regulating mood.^[41,42]

CONCLUSION

Based on the information presented, it could be concluded that clove represents a very interesting plant with an enormous potential as analgesic and helpful in opiate de addiction in Sickle Cell Disease by virtue of its properties, chemical components and unique aroma.

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