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Fentanyl Iontophoresis Can Facilitate Early Physiotherapy in Post Surgical Acute Pain: A Literature Review

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ABSTRACT

Background: Iontophoresis is a technique of transferring ions into the tissues through the skin by using direct current. It can serve as a substitute for chemical enhancer, eliminates toxicity and adverse reaction formulation problems associated with chemical enhancer.
Purpose: The purpose of this literature is to review the studies to see the effectiveness of Fentanyl Iontophoresis in the post operative acute pain and also to find out whether it helps in facilitating the physiotherapy in the post operative acute phase.
Methods and Materials: The database literature search was carried out in the electronic database - Medline, and Research gate. Iontophoresis, Post-operative acute pain, Fentanyl Iontophoresis were the key words used to search in the electronic database. Randomized control trials, systematic review, meta-analysis, and case studies included into the review.
Conclusion: Fentanyl iontophoresis system offers safety advantages in terms of opioid related drug adverse events (ORADEs) compared with morphine (iv) patient controlled analgesia for the management of acute postoperative pain. Fentanyl iontophoresis is highly potent and capable in relieving the post operative acute pain. This system of transferring ions into the tissues through the skin can play important role in initiating early physiotherapy and improve the mobility and functional limitations of the patient.

Keywords: Iontophoresis, Post-operative acute pain, Fentanyl Iontophoretic System.

INTRODUCTION

The stratum corneum layer acts as a barrier to entry to any kind of therapeutic entities if administered through the skin and retards bioavailability. Therefore, a variety of strategies have been adopted for the enhancement of transdermal permeation for drug delivery and biosensing of various substances. Physical techniques such as iontophoresis, reverse iontophoresis, electroporation, and microneedles offer (a) electrical amplification for transdermal sensing of biomolecules and (b) transport of amphiphilic drug molecules to the targeted site in a minimally invasive manner [(1)].

Iontophoresis is the noninvasive, sterile and relatively painless technique of transferring medically useful ions into the tissues through the skin by using direct current [(2)]. The method of Iontophoresis was described by Pivati in 1747 [(3)], however, the method of administering pharmacological agents by Iontophoresis became popular at the beginning of 20th century due to the

work of Leduc (1900) who introduced the term iontotherapy and formulated the laws for this process. [4] The use of Iontophoresis can serve as a substitute for chemical enhancer [5] eliminates toxicity, adverse reaction formulation problems associated with chemical enhancer in pharmaceuticals [6].

Principle

Iontophoresis is based on the principle that an electrically charged electrode will repel similarly charged ions. The technique really gained momentum, through its use since that time has been sporadic reference from basic principles. It increases permeation of ionic drugs, provides programmable drug delivery [7][8] improves patients compliance with electronic reminders, allows patient-specific delivery controlled by current adjustments [1]. Iontophoresis uses low intensity current with controlled delivery of ionized drugs through the skin into the tissues. [9]

Mechanism

To drive the drugs into the tissues through the skin a direct galvanic current is used. However, some authorities suggest that the current should be continuous, though others argue that so long as the current is monophasic in nature, a pulsed application can be used. Essentially, the substance (medication or bioactive agent) needs to be driven into the tissues must be ionic in nature. The substance or drug must be placed under the electrode with the same charge. Usually, there are two charged electrode chambers; the positively charged chamber, called the anode and the negatively charged chamber called the cathode. The anode will repel the positively charged drugs ions, whereas, the cathode will repel negatively charged drug ions. Conventionally, the ionic solution is placed under the active electrode, also called as treatment or delivery electrode and the other electrode is used to complete the circuit, known as indifferent, dispersive, inactive or return electrode.

If delivery of positively charged drug is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity [3]. Application of direct current would repel the ions into the tissues through the skin. The ions are driven into the skin through the pores, hair follicles, sweat gland ducts – rather through the stratum corneum. The ducts are the route of preference as they allow greater passage of current due to lower electrical resistance than the stratum corneum. The smaller and more hydrophilic ions are transported at a faster rate than larger ions [10][11][12]. The permeability coefficient decreases as the size of the molecules increases [13]. The studies have shown that the transport of the compounds into the tissues through the skin is decreased as the weight of the molecules is increased. This can be arranged in the decreasing order of the transportation as follows - chloride> amino acid >nucleotide > tripeptide >insulin [14][15][16][15].

Clinical Uses

Hyperhidrosis

Palmar hyperhidrosis (PH) is characterized by excessive hand sweating beyond normal thermoregulatory needs, which may either be primary or secondary. Primary PH is attributed to localized sympathetic hyperactivity on otherwise normal eccrine sweat glands, mainly triggered by emotional or thermal stimuli. Secondary PH is a pathological or mainly occurs due to over use of the medicines [17][18]. Tap water iontophoresis has long been recognized to successfully inhibit palmer sweating (hyperhidrosis) [19]. Both the hands are submerged in shallow water tub or tray. The electrodes are placed on the palmer aspect with an appropriate distance. A mild direct current with an intensity of 15-20 milli ampere is applied for a period of 15-40 minutes depending on the device [20][18]. The procedure is initially performed 3-4 times per week until the desired effect has been achieved for the period of 3-4weeks, thereafter, the patients are switched

to a maintenance schedule of once every 1-4weeks [17][21].

Diabetic Ulcers and Wounds

The zinc sulfate Iontophoretic current is able to consistently improve the morphological and ultra-structural changes seen in the healing of diabetic animal's process, even when the hyperglycemic state is maintained [22]. Zinc Sulphate iontophoresis also had beneficial effect on the mechanical resistance of scars produced in the skin of diabetic rats. This therapeutic effect may play an important role in reducing the complications which occur due to surgical wounds of the skin in diabetic subjects, mainly in most vulnerable stages of incisions to dehiscence, leakages and infections [23] The histamine Iontophoresis can be used as in vivo model to elicit local and acute skin inflammation with minimal impact on the skin barrier, in contrast to tape stripping and topical application of irritants in which the skin barrier is disrupted either mechanically or chemically [24].

Dentinal Hypersensitivity

Dental hypersensitivity is caused due to non-noxious stimuli. The prevalence of hypersensitive in India is about 20.06%, which is more commoner in the females, however, symptoms may reduce later in life, due to age related dentin and pulpal changes [25]. The agents such as potassium nitrate, calcium compound are practiced for its management. The study conducted by Kumar and colleagues (2020) suggested that topical application of Colgate sensitive pro-relief (contains 8% arginine-calcium carbonate). Iontophoresis can cause deeper penetration of the ions thus giving a better sealing effect. Hence, it can be used as the first line of treatment in severe dentinal hypersensitivity [26].

Spinal Cord Injury Bowel Movement

Neurogenic bowel is a common complication of spinal cord injury which is characterized by difficulty in evacuation of bowel, abdominal pain, and fecal incontinence. There is slowing of peristaltic contraction in the recto-sigmoid colon in patients with the spinal cord injury most likely the result of down-regulation of parasympathetic neural pathways leading from the central nervous system of the gut. Neostigmine (NEO) initiates high amplitude peristaltic contractions in the recto-sigmoid colon. Transdermal administration of neostigmine/glycopyrrolate by iontophoresis appears to be a practical, safe, and effective approach to induce bowel evacuation in individuals with spinal cord injury [27].

Post-Operative Acute Pain

Acute pain management following surgical interventions has been remained a problem for the clinicians due to complications such as thromboembolic and pulmonary. It is associated with prolong stay in the hospitals, impairment in quality of life, and the potential to develop chronic pain [28]. All these may lead to increase emotional stress and health care costs [29]. Transdermal delivery of lidocaine for anesthesia and fentanyl for post-operative pain through the iontophoresis process was also explained [30]. However, we did not find the study, which has shown fentanyl to be significantly superior to others drugs. Hence, the purpose of our study is to review the studies to see the effectiveness of fentanyl Iontophoresis in acute post operative pain and how this can facilitate the early physiotherapy.

METHODS AND MATERIAL

Search Strategy

The database literature search was carried out in the following database Medline, and research gate to search the potential studies for the literature. The language of the studies was restricted to the English. The search was performed using keywords – iontophoresis, iontophoresis fentanyl system, fentanyl drug and post-operative acute pain in the electronic data base. The title and abstracts of the literatures were reviewed and chose the potential ones.

The related articles selected according to the inclusion and exclusion criteria.

Study Design

The literature review included the Fentanyl Iontophoresis studies in the post operative acute pain. Randomized Controlled Trials (RCTs), Meta-analyses, Systematic Reviews, pilot studies, and Case Studies, conducted on the fentanyl Iontophoresis in the management of acute post-operative pain were included.

DISCUSSION

The fentanyl Iontophoretic system is a needle-free, patient controlled analgesic system that is used for the management of acute, moderate-to-severe postoperative pain in hospitalized adult patients. The patient activates the system by pressing the recessed dosing button twice within the three seconds. Activation of the system produces low intensity electric current of 170 micro ampere. Positively charged fentanyl molecules within the anode hydrogel reservoir are then repelled from the positively charged anode surface and delivered transdermally into the systemic circulation. The system delivers a pre-programmed 40 microgram dose of fentanyl for the period of 10 minutes. Patient may self-administer a maximum of six doses in an hour. ITS functions for up to 24 hours and delivers maximum of 80 doses after that it stops functioning automatically. System is replaced with the new one and three such systems can be used for the maximum period of 72 hours [(31)].

The food and drug administration (FDA) approved the fentanyl HCL Iontophoretic transdermal system (ITS) in 2006. The novel Iontophoretic technology propels ionized fentanyl molecules into the vasculature, as opposed to just relying on passive diffusion [(31)]. IONSYS, The Medicines Company, Parsippany, NJ, USA produces fentanyl Iontophoretic System was approved by both the United States Food and Drug Administration and the European Medicines Committee in April 2015 and November 2015 respectively for the management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital [(32)]. The ideal property for the drug to be delivered through Iontophoresis (transdermal) is low molecular mass and high lipid solubility [(33)]. Fentanyl Hydrochloride has a lower molecular weight (372Da) whereas, the molecular mass of morphine sulfate is 758Da [(34)]. In addition to that the fentanyl is 100 times potent than the morphine and enters into the CNS 133 times easier than the morphine. Fentanyl is metabolized to inactive metabolites whereas; the morphine is metabolized to active metabolites [(34)]. Fentanyl Iontophoresis can be used only in patients who have an appropriate respiratory function and adequate cognitive ability. Additionally, as per the prescribing information, fentanyl ITS is to be used after patients have been titrated to an acceptable level of analgesia, typically using alternate opioid analgesics [(32)].

A separate validated Ease of Care (EOC) Questionnaire was designed for the nurses [(35)], the physical therapist [(36)], and for the patients [(37)] to see the improvement in the mobility of the patients. The fentanyl system has been found to improve mobility as assessed not only by the patients but also by the nurses and physical therapist. The facilitation of physical therapists' functioning may translate into an improved rehabilitation experience [(38)].

Diane et al. conducted an analysis of the four studies to see summative usability evaluations, including behavior and subjective evaluation for the fentanyl Iontophoretic transdermal system (ITS). They found that the patients, nurses, and pharmacists were able to use fentanyl ITS with ease [(39)]. A meta-analysis of randomized controlled trials was conducted to compare the efficacy and safety of patient-controlled fentanyl Iontophoretic transdermal system (ITS) with morphine intravenous (iv) patient-controlled analgesia (PCA) for pain management following gynecological surgery. They included two

studies which had patients who had undergone gynecological, orthopedic, thoracic or other major abdominal surgeries. The study found that following gynecological surgery, patients and investigators were more satisfied with fentanyl ITS than morphine iv. Patient controlled analgesia as a method of pain [(40)].

Fentanyl iontophoresis system offers safety advantages in terms of opioid related drug adverse events (ORADEs) compared with morphine IV. Patient controlled analgesia for the management of acute postoperative pain. [(41)(42)(43)(44)]

CONCLUSION

Fentanyl Iontophoretic System (FIS) is a non-invasive, safe and more potent than the morphine i.v. patient control analgesia for the management of post-operative acute pain, and can be administered by the patient himself or herself. This system of transferring ions into the tissues through the skin can play important role in initiating early physiotherapy and improve the mobility and functional limitations of the patient. The opioid related adverse drugs events (ORADE) and post operative complications such as pulmonary and deep venous thrombosis can be prevented by early mobilizing the patient.

We found only few studies on the effectiveness of fentanyl iontophoresis in post operative acute pain. Further, high quality randomized controlled trials needed to see the effectiveness of fentanyl iontophoresis in post operative acute pain.

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Authors' Contributions

Roshan Lal Meena conceived of the presented idea. Roshan Lal Meena developed the theory and performed the computations. Tarun Kumar verified the analytical methods and referencing. Thaiba Reinai article searching of this work. All authors discussed the results and contributed to the final manuscript

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