DOI: https://doi.org/10.53350/pjmhs22163703

ORIGINAL ARTICLE

Iontophoretic Transport of Local Anesthesia: A Literature Review

NAFEESA TABASSUM[1]
[1]*College Of Dentistry, DSDS Department, Dar Al Uloom University,Riyadh, Kingdom of Saudi Arabia.*
Corresponding author: Nafeesa Tabassum, Email: nafeesa.t@dau.edu.sa

ABSTRACT

Aim: This study aimed to comprehensively review the literature about the use of iontophoresis for the transportation of local anesthesia to better understand the feasibility of such technique and its benefits compared to other delivery systems. In addition, in the current review we present the challenges compromising the use of this drug delivery system in this area.

Material and Methods: This is a literature review which aimed to screen old as well as very recent literature on the technique, methodology, clinical findings, influencing factors of local anesthetics iontophoresis, thus PubMed electronic databases were screened. Indexed articles during the time period extending between 1977 and 2021 were tentatively reviewed.

This review was registered by and it only included articles written in English. Research studies conducted in vitro or on animals were excluded in addition to case studies, case series, and pilot studies. Articles that included major forms of bias were also excluded.

Pubmed database was screened using the following Mesh terms: Anesthetics, Local / administration & dosage*, Epinephrine / administration & dosage, Ethanol / pharmacology, Humans, Iontophoresis*, Lidocaine / administration & dosage, Regional Blood Flow, Skin / blood supply, Skin / drug effects*Skin / metabolism.

Results: A total of 89 studies were screened for possible inclusion after searching for the above mesh terms in PubMed. Eventually, 16 articles were included in this review where 2 studies were related to iontophoretic anesthesia of the ear, 6 were related to skin anesthesia, and 7 related to the oral cavity. The other three studies compared the use of local anesthesia mediated by iontophoresis to other approaches and the change in dosing requirements following iontophoresis administration of local anesthetics.

Keywords: Pain management, local anesthesia, drug delivery system, transport, Iontophoresis.

INTRODUCTION

Use of anesthetics in dental practice: Anesthetics are widely used in dental and clinical practice to mitigate pain accompanying performed procedures. Local anesthesia includes the direct injection of the skin or muscle or application of an anesthetic agent where pain will mostly occur. Generally, local anesthetics include injectable, topical, dental (non-injectable), and ophthalmic. Administration of topical anesthetic before injecting the area with a similar agent is a common practice in dentistry to reduce pain precipitated by needle insertion, thus offering pain-free dental anesthesia. Additionally, local anesthetics are used to mitigate pain and discomfort associated with oral lesions (1). Nevertheless, not all formulations are successful in achieving such a goal due to drug dilution and rapid elimination by the saliva; drug distribution; and poor drug permeation across the membrane barriers. In fact, the oral mucosa epithelium barrier had been wrongly assumed to be a highly permeable tissue. Thus, formulating anesthetics in an efficient drug delivery system (DDS) has always been the focus of research to overcome these shortcomings, enhance permeability, and to mitigate clinical mis conveniences and dentists' nervousness. While the short duration of anesthetics, due to their redistribution from the injection site, is considered a major problem, the penetration of the latter remains a challenging feature to address.

Anesthetics' advancements: During the past 100 years, advancements in local anesthetic techniques were deemed the most crucial changes happening to dental science. DDS includes chemical approaches, such as nanostructured carriers (e.g., encapsulation in liposomes, complexation in cyclodextrins, or their association with other nanoparticle biopolymers), the addition of permeation enhancers, or formulating the agent in a specialized dosage form (e.g., patches, bio- and mucoadhesive systems, and hydrogels). DDS also comprises physical methods (e.g., pre-cooling, vibration, iontophoresis, and microneedle arrays) or a combination of both means which is considered a preferred option in oral mucosa. Yet, further studies are still needed to investigate the effectiveness of the aforementioned combination. The following are also examples of the newer delivery methods that are utilized in modern dentistry: Electronic Dental Anesthesia (EDA), Intra-oral Lidocaine Patch (DentiPatch ®, Jet Injection, Eutectic Mixture of Local Anesthetics (EMLA), Computer Controlled Local Anesthetic Delivery Devices (CCLAD), Intraosseous Systems (IO Systems), and Iontophoresis. Currently published clinical trials indicate that the use of liposomal encapsulation and the pre-cooling technique has promoted the efficacy of topical anesthetics in different oral mucosal sites, including the palatal mucosa.

Iontophoresis: Through the generation of an electric field across the targeted area's membrane (i.e., direct-field effect), iontophoresis non-invasively enhances the systemic and local delivery of both ionic and neutral drugs. Electroosmosis (i.e., Electroosmotic solvent flow that drives charged and neutral molecules across a charged membrane), and electro permeabilization (i.e., it increases the membrane's intrinsic permeability through altering its properties: pores' charges and sizes) are other mechanisms adopted by iontophoresis (2,6). Those mechanisms are usually well studied in the skin, cornea and sclera, and nails (3,6-9), but not in the oral cavity. Direct-field effect and electroosmosis were thought to be the main mechanisms in buccal iontophoretic transport (10). Ren et al. (11) noted that for ionic compounds direct-field effect was the dominant flux-enhancing mechanism; however, for neutral and ionic permeants electroosmosis was found to be accountable.

The use of iontophoresis in clinical practice: Several iontophoresis treatments have been approved by the US Food and Drug Administration (FDA) including transdermal fentanyl (Ionsys) in 2015 (12,13), sumatriptan (Zecuity) in 2013, (14,15), topical pilocarpine for sweat stimulation (Nanoduct) (16,17). Other off-label uses of iontophoresis include the administration of dexamethasone for rehabilitation during physical therapy (18).

Approved iontophoretic local anesthetics: Iontophoresis anesthetics have also been approved by the FDA for local skin anesthesia. These include topical lidocaine (e.g., Iontocaine and Lidosite) (19,20), and trans tympanic lidocaine for tympanic membrane anesthesia (21,22).

The use of iontophoresis in the oral cavity: Research has primarily focused on iontophoresis facilitation of administration of topical agents or trans-buccally administered systemic medications. Upon its buccal application, a significant improvement in drugs' transportation in comparison with passive drug diffusion was noticed for different medications. Likewise, iontophoresis improved the topical penetration of medications into both soft and hard oral tissues (i.e., enamel, dentin, and oral mucosa). These techniques generally help prolong the drug release and exposure time at the sites of action. Commonly used topical anesthetics require 30 to 60 minutes to impart effective anesthesia. The novel low-dose lidocaine iontophoresis system (LDLIS) may provide

topical anesthesia in 10 minutes at a lower dose compared to other systems, thus limiting adverse events.

In dentistry, the use of such technique was mainly tested to produce efficient local anesthesia and to treat tooth decalcification and hypersensitivity. Gangarosa described the use of iontophoresis in dentistry as follows (23):

1 Treatment of hypersensitive dentin (e.g. - in teeth sensitive to air and cold liquids) using negatively charged fluoride ions.

2 Treatment of oral ulcers ("canker sores") and herpes orolabialis lesions ("fever blisters") using negatively charged corticosteroids and antiviral drugs, respectively; and

3 The application of local anesthetics to produce profound topical anesthesia, as is done in some physical therapy applications.

In this regard, iontophoresis of the enamel along with the administration of fluoride and peroxide can effectively treat decalcification and teeth whitening. More importantly, iontophoresis can be employed to deliver local anesthetics to oral mucosal tissues prior to oral procedure. However, less is known about the gingival iontophoresis of antibacterial and anti-inflammatory agents to control the progression of periodontal diseases. Under the identified research conditions, the use of iontophoresis was found to be safe according to studies investigating its use in the human oral cavity (24,25). Nonetheless, the use of iontophoresis in dental practice remains strictly limited because of the less developed knowledge on the applicability and effectiveness of such method in the oral cavity compared to other routes of administration (e.g., transdermal and ocular iontophoresis). The limited knowledge on gingival drug permeation is the best example in this matter. Furthermore, although several studies have reported promising in vitro performance, the literature is still poor in clinical trials which only tested a few formulations.

Thus, this study aimed to comprehensively review the literature about the use of iontophoresis for the transportation of local anesthesia to better understand the feasibility of such technique and its benefits compared to other delivery systems. In addition, in the current review we present the challenges compromising the use of this drug delivery system in this area.

MATERIAL AND METHODS

This is a literature review which aimed to screen old as well as very recent literature on the technique, methodology, clinical findings, influencing factors of local anesthetics iontophoresis, thus PubMed electronic databases were screened. Indexed articles during the time period extending between 1977 and 2021 were tentatively reviewed.

This review was registered by and it only included articles written in English. Research studies conducted in vitro or on animals were excluded in addition to case studies, case series, and pilot studies. Articles that included major forms of bias were also excluded.

PubMed database was screened using the following Mesh terms: Anesthetics, Local / administration & dosage*, Epinephrine / administration & dosage, Ethanol / pharmacology, Humans, Iontophoresis*, Lidocaine / administration & dosage, Regional Blood Flow, Skin / blood supply, Skin / drug effects*Skin / metabolism.

RESULTS

A total of 89 studies were screened for possible inclusion after searching for the above mesh terms in PubMed. Eventually, 16 articles were included in this review where 2 studies were

related to iontophoretic anesthesia of the ear, 6 were related to skin anesthesia, and 7 related to the oral cavity. The other three studies compared the use of local anesthesia mediated by iontophoresis to other approaches and the change in dosing requirements following iontophoresis administration of local anesthetics.

Table 1: Iontophoretic administration of local anesthetics

Study	Year of publicati on	Aims and outcomes	Conclusion
Otorhinolaryngology			
Comeau et	1973	Outcomes: Depth of anesthesia	Lidocaine Iontophoresis of the human's external ear produced eardrum anesthesia. The depth of anesthesia was adequate to permit the execution of painless myringotomies.
T Brusis and I Loennecken (27)	1985		Tinnitus was reduced completely or partially in 31 patients after repeated iontophoresis application to one or both ears.
			No connection was seen between therapy failure and the origin of the tinnitus where treatment was unsuccessful in 19 cases.
			No serious adverse effects were seen.
Skin			
J Russo Jr et al.	1980	Aim:	Lidocaine iontophoresis
(28)		To test the duration of	produced local anesthesia of
		anesthesia after the	significantly longer duration
		administration of either	than topical application of
		lidocaine or placebo by iontophoresis, subcutaneous infiltration, or swabbing Outcomes: The duration and depth of anesthesia Population: Flexor surface of each forearm of 27 subjects.	lidocaine or placebo by any route of administration, but of significantly shorter duration than lidocaine infiltration. Lidocaine iontophoresis produced local anesthesia for about five minutes without requiring the use of ahypodermic needle and syringe.
Maloney et	1992	Aim: To determine the practicality of lidocaine iontophoresis prior to invasive procedures in dermatology offices using 4% lidocaine with epinephrine 1:50,000 iontophoresis.	Local anesthesia iontophoresis was 80 to 100% effective for pain associated with the following procedures (e.g., injections, abrasions, laser surgery, and cautery) iontophoresis was less effective for pain relief associated with dermal excisions.
M A Ashburn et al. (30)	1997	Aim: To evaluate the clinical safety and effectiveness of the iontophoretic administration of lidocaine HCl 2% and epinephrine 1:100,000 to induce local dermal anesthesia before intravenous (i.v.) cannulation. Outcomes: Venous blood plasma lidocaine levels and	No detectable lidocaine was identified in blood. Adverse effects were minimal and transitory. Pain was minimized following lidocaine iontophoresis compared to controls as claimed by both the patients and investigators. Short delivery times of 2% lidocaine Iontophoresis with 1:100,000

		adverse events associated with iontophoresis. Patient and investigator assessment of analgesia and patient acceptance of the procedure.	epinephrine does not lead to delivery of lidocaine to the systemic circulation in healthy adults.
P J Sadler et al. (31)	1999	Aim: To compare iontophoretic and local lidocaine for pain	Pain scores on cannulation were significantly less in the
		relief prior to propofol injection. Outcomes: Pain was assessed on insertion of a 20-gauge i.v. cannula and at 10-s intervals for 30 s after injection of propofol.	iontophoresis group control group ($P < 0.005$). Pain after injection of propofol was significantly reduced at 10 ($P < 0.002$), 20 ($P < 0.001$) and 30 s ($P < 0.001$). Iontophoretically applied lidocaine depleted the pain accompanying cannulation and propofol injection.
Jeffrey L Galinkin et	2002	Aim: To compare dermal analgesia produced by lidocaine iontophoresis and eutectic mixture of local anesthetics (EMLA). Outcomes: Pain during venipuncture was assessed by the subject, parent, observer, and technician performing the procedure using the 100-mm visual analog scale. The Children's Hospital of Eastern Ontario Pain Scale to rate the subject's pain was also utilized. Ratings of subject satisfaction were also assessed. population: 22 healthy patients	No significant difference was noted between the two groups in the subject-rated visual analog scale or the Children's Hospital of Eastern Ontario Pain Scale scores. 50% of the 22 subjects who completed both sessions preferred iontophoresis. 23% of them preferred EMLA, and 27% had no specific preference. Lidocaine iontophoresis is a useful noninvasive alternative to establish dermal analgesia for venous cannulation and it provides similar pain relief compared to EMLA.
Tania D Strout et al. (33)	2004	Aim: To compare the efficacy and feasibility of a collaborative iontophoresis procedure for dermal anesthesia prior to	Dermal anesthesia by lidocaine iontophoresis in patients undergoing a LP takes longer but decreases the pain associated with the
		lumbar puncture (LP) in adult ED patients. Outcomes: Pain was assessed at 3 points using an 11-point numeric rating scale to measure pain, and provider satisfaction.	administration of anesthesia, thus increasing provider satisfaction.
Oral cavity			
T Petelenz, et al. (34)	1984	Aim: To test the efficacy and safety of 2% solution of lignocaine iontophoresis for 10 min at a current of 1-2.5 mA.	76% of injections were pain free after lidocaine iontophoresis. Following placebo iontophoresis, 87% of injections were painful. Iontophoresis using the mini set effectively protected the patient against injection pain. The electronic structure of the device makes it possible for safe outpatient use.
Irsfeld S. et al (35)	1993	Aim: To compare the efficacy of EMLA cream with 5% lignocaine-adrenaline 1:50,000 iontophoresis Outcomes: Depth of tissue penetration and pain caused by i.v. needle injection.	Local anesthetics deeply penetrate and numbed both veins and skin with iontophoresis only. Pain was abolished after i.v. injection in five of six volunteers whereas EMLA had no effect
Hideharu Ikeda, Hideaki Suda (36)	2013	Aim: To evaluate the chemical permeability through human enamel/dentine using conductometry and to clarify if alternating current (AC) iontophoresis facilitates such permeability.	Lidocaine levels that passed through enamel/dentine were increased by AC iontophoresis as detected by the conductometry
		Outcomes: The change in the concentration of lidocaine hydrochloride in the pulp-side chamber was measured every 2min using a platinum recording probe positioned at the Centre of the pulp-side chamber. Passive entry without iontophoresis was used as a control.	
Camila Cubayachi et al. (37)	2015	Aim: To assess the effect of iontophoresis in the mucosal penetration of prilocaine hydrochloride (PCL) and lidocaine hydrochloride (LCL), when combined together. Outcomes: The distribution coefficients between the mucosa and the formulations (Dm/f) along with the mucosal permeation and retention rates.	Iontophoresis boosted the permeation rate of PCL by 12-fold across the mucosa but did not significantly affect LCL influx. Combining the drugs also resulted in an 86 fold increase in PCL levels in the mucosa and 12 fold incline in those of LCL after iontophoresis at pH 7.0 compared with either drug administration by iontophoresis This strategy can serve as a needle-free strategy to speed up the onset and extend the duration of buccal anesthesia. Buccal iontophoresis may offer a pain free replacement of the painful anesthesia injections.
Watchana Thongkukiatkun et al. (38)	2015	Aim: To determine the impact of lignocaine and epinephrine iontophoresis on the sensitivity of human dentine Outcomes: Dentine sensitivity was tested with probing and air blast stimuli.	The lignocaine plus epinephrine solution completely blocked the pain produced by both forms of stimulus immediately, and this continued for at least 40 min. An immediate fall in pulpal blood flow was also detected which also lasted for at least 40 min.
		Subjective assessment of pain was done on a score from 0-100. The sensitivity of the dentine was tested before and after the treatment.	The epinephrine solution had a similar impact on pulpal blood flow but not on dentine sensitivity. This method can foster dentine anesthesia without the use of an injection.

		Pulpal blood flow was recorded at each stage.	
The Late Korporn Smitayothin	2015	Aim: To determine the effectiveness of lignocaine-epinephrine iontophoresis through carious dentine for pain control during the process of cavity preparation. Outcomes: Subjective assessment of pain intensity on visual analogue scale (VAS). A current of 200 µA was applied for 2–10 min in 56 carious molars.	The total duration of iontophoresis required to anaesthetize the dentine was (minutes): 2 in 7 teeth, 4 in 17 teeth, 6 in 14 teeth, 8 in 4 teeth, and 10 in 7 teeth. seven teeth were not anaesthetized even after 14 min of iontophoresis application.. Lignocaine-epinephrine iontophoresis anaesthetized dentine in 87.5% of carious molars.
Do Couto et al. (40)	2021	Aim: To develop a mucoadhesive iontophoretic patch for anesthetic delivery in the buccal epithelium. Outcomes: Drug release kinetics and drug permeation through the porcine esophageal epithelium	Buccal iontophoretic patch displays a favorable strategy for pain and needle free local anesthesia in dentistry. Iontophoresis remarkably enhanced the permeation and retention of local anesthetics (mainly prilocaine)

Table 2: Comparison of local anesthesia mediated by iontophoresis compared to other approaches.

Article	Year	Aim	Conclusion
M S Wallace et al. (40)	2001	Aim: To compare the onset, duration, and depth of local anesthesia after the topical lidocaine delivery using electroporation (EP), electroincorporation (EI), and iontophoresis (IP) Outcomes: Onset and duration of anesthesia assessed by: warm sensation cool sensation hot pain Depth of anesthesia was determined by measuring pain sensation in response to a 27-gauge needle.	Lidocaine transdermal delivery by IP, EP, and EI resulted in similar surface skin anesthesia IP resulted in deeper anesthesia. Plasma lidocaine levels were undetectable.

Table 3: Change in dosing requirements following iontophoresis administration of local anesthetics

Article	Year	Aim	Conclusion
T Oshima et al. (42)	1994	Aim: To assess the high concentration iontophoresis of lidocaine. Outcomes: The response to pin prick with a 27-gauge sterile needle inserted to a depth of 2 mm at five random locations in the iontophoretically-stimulated area. Venous lidocaine levels were measured at 3, 10, and 30 min after iontophoresis with lidocaine 50%.	The pain score after five-minute iontophoresis was higher than that after ten-minute iontophoresis whereas the pain scores were not associated with lidocaine concentration within five-minute and ten-minute iontophoresis groups. Plasma lidocaine concentration was minimal in all samples. No side effects other than erythema were detected following high concentrations of lidocaine (50%) iontophoresis. By increasing lidocaine concentration up to 50%, iontophoresis application time could not be reduced from ten to five minutes.
Neal RGlaviano et al. (41)	2011	Aim: To compare high-dose lidocaine iontophoresis with standard-dose lidocaine	The standard dose (40-mA-min) treatment was just as effective as the high dose therapy (80-mA-min). Shorter treatments are more time efficient.
		iontophoresis by measuring skin anesthesia.	

All finally selected articles for the review were done in vivo on humans and were released in English with a detailed description of their research methodology and participants characteristics. All studies were published over the period extending between 1973 and 2021 and included a variety of patients to ensure statistical validity.

Reliability of studies: The reliability of a study is highly modulated by the number of patients treated, baseline patients characteristics, methods used, and the bias within selected studies.

DISCUSSION

The anesthetic iontophoretic system is a non-invasive pain-free method of anesthesia administration which was first suggested in 1993 as a possible substitute for drug application in promoting local anesthesia. Although this technique was not always backed up by science, it has been previously used by physical therapists for rehabilitation to reduce inflammation accompanying musculoskeletal disorders through iontophoretic dexamethasone application. More recently, this technique has undergone meticulous investigations and gained copious FDA approvals and patients' attention as it offers better compliance rates and side effect profile (i.e., non-invasive). Through the utilization of a constant low-voltage direct current, this approach transports the drug through the skin by promoting ion transport. Positively charged lignocaine molecules are thus transported through repulsive force caused by the positive electrode (44).

However, higher current or longer exposure can cause skin irritation. More importantly, the prolonged exposure to direct current, electrochemical polarization occurs in the skin. This causes a decline in the magnitude of current flow through the skin, thereby affecting the amount of delivered drug ions (45).

Currently, the FDA does not approve the use of any oral iontophoretic anesthetic system. Such local anesthetics are however approved by the FDA through other routes of administration. In 2004, the FDA approved the use of Lidocaine-epinephrine combination (Lidosite®). Coadministration of epinephrine decreases lidocaine requirements through reducing the drug clearance (i.e., vasoconstriction) and prolongs the anesthetic duration of action (46). Lidosite® is applied for 10 min with a patch at which both lidocaine and epinephrine are positively charged (46).

For local drug delivery into the oral cavity, iontophoresis could ultimately enhance a drug's penetration into soft and hard oral tissues including the enamel and the dentin. The difference in oral cavity structures and characteristics accounts for a major difference in the barrier properties and permeabilities of drugs. The oral mucosa comprises the buccal, sublingual, and gingival mucosa. The sublingual mucosa and the buccal mucosa are to some extent similar, but the former is thinner with less layers of epithelial cells.

Buccal drug delivery by means of iontophoresis was proposed to be safe under the studied conditions in vivo studies (24,25). No adverse effects were noted after buccal iontophoresis treatments that delivered 0.21 mA (2 mA/cm2) for 10 min in these

studies. Investigated drugs included prilocaine and lidocaine for local anesthetics in dentistry (37). These studies have demonstrated an enhanced drug delivery when iontophoresis was manipulated **(Table 1)**.

Limited studies are available on the use of iontophoresis for cornified oral mucosa (e.g., palate and gingiva). Such areas are anatomically varied from the buccal mucosa where the cornified epithelium is thought to be less permeable in comparison with the buccal mucosa.

The reviewed treatments were conducted at slowly increasing electric current or until the patient first felt a minute tingling sensation. Higher current dose (e.g., 1.0 mA) for 5 min has also been used. Iontophoresis was shown to be safe in those studies. The safety of iontophoresis was further illustrated in Chinnapareddy et al.'s study where an iontophoretic toothbrush delivering electric current (0.4 mA for 2 min) reported no in vivo adverse effects in the oral cavity (47). In this study, Chinnapareddy assessed the correlation between the voltage and electric current for enamel iontophoresis in humans (47). The association between time of application of the current and its intensity and the number of moles of the transported ion was also described by Faraday's Law states. Other factors that may influence the iontophoretic transfer include the drug concentration (linear then reaches plateau) (48), physicochemical properties of the molecule (i.e., size, partition coefficient, and charge) (48), and the pH of the solution. Generally, small and hydrophilic molecules are more easily transported compared to larger and lipophilic molecules (48).

Smitayothin et al. introduced the anesthetized effect of lignocaine-epinephrine combinational iontophoresis (200 mA current was applied for 2 min) on dentine for cavity preparation. Time of iontophoresis application required to anaesthetize the dentine varied from: Two min to 10 min. More than three quarters (87.5%) of the studied molars were anesthetized by lignocaine-epinephrine iontophoresis (39). Another study reported that the use of iontophoretic lignocaine- epinephrine combination for tooth caries promptly mitigates pain and lasts for at least 40 min (38). Without iontophoresis, local 50% lignocaine solution produces anesthesia after a latent period for up to 30 min and only lasts for 10 min (49). The addition of epinephrine significantly boosts and prolongs the anesthetic effect of lidocaine during iontophoresis.

It is worth mentioning that direct current delivers lidocaine more rapidly in comparison with alternating current as presented by Inoue et al. Alternating current iontophoresis was also proven to transfer lidocaine hydrochloride through enamel/dentine (36). Saliba et al. indicated that the anesthetic level is not impacted by high amplitude/short duration or low amplitude/long duration of lidocaine iontophoresis as long as the same dosage is applied (50).

Cost-effectiveness: The increased expense associated with iontophoretic devices compared to the usual topical formulations makes iontophoresis of less use although there is limited data about its cost-effectiveness. Some studies have been, however, in favor of iontophoresis. A cost-effectiveness study, analyzing the use of various anesthetic agents for the reduction of pain associated with peripheral intravenous cannulation, reported the superiority of lidocaine iontophoresis over lidocaine/prilocaine cream but not over needle-free lidocaine jet injection device71.

CONCLUSION

It is evident from this review that anesthetic iontophoresis systems offer safety advantages in terms of decreased adverse events related to needle injection and a deeper local anesthesia sparing systemic exposure. This holds a lot of promise for the future of drug delivery systems. Using iontophoresis, local anesthetic delivery has been demonstrated to be both safe and efficient.

Funding: This research received no external funding.
Conflicts of Interest: Single author-no Conflicts of Interest
Acknowledgment:: The author extends appreciation to the Deanship of Postgraduate and Scientific Research at Dar Al Uloom University for their financial support of this work.

REFERENCES

1. Franz-Montan M., Ribeiro L.N.M., Volpato M.C., Cereda C.M.S., Groppo F.C., Tofoli G.R., de Araujo D.R., Santi P., Padula C., de Paula E. Recent advances and perspectives in topical oral anesthesia. Expert Opin. Drug Deliv. 2017;14:673–684. doi: 10.1080/17425247.2016.1227784.
2. 30. Kasting G.B. Theoretical models for iontophoretic delivery. Adv. Drug Deliv. Rev. 1992;9:177–199. doi: 10.1016/0169-409X(92)90023-J. [CrossRef] [Google Scholar]
3. 31. Kalia Y.N., Naik A., Garrison J., Guy R.H. Iontophoretic drug delivery. Adv. Drug Deliv. Rev. 2004;56:619–658. doi: 10.1016/j.addr.2003.10.026. [PubMed] [CrossRef] [Google Scholar]
4. 32. Pikal M.J. The role of electroosmotic flow in transdermal iontophoresis. Adv. Drug Deliv. Rev 2001;46:281–305. doi: 10.1016/S0169-409X(00)00138-1. [PubMed] [C rossRef] [Google Scholar]
5. 33. Costello C.T., Jeske A.H. Iontophoresis: Applications in transdermal medication delivery. Phys. Ther. 1995;75:554–563. doi: 10.1093/ptj/75.6.554. [PubMed] [CrossRef] [Google Scholar]
6. 34. Li S.K., Hao J., Liddell M.R. Electrotransport across membranes in biological media: Electrokinetic theories and applications in drug delivery. In: Becker S., Kuznetsov A., editors. Transport in Biological Media. 1st ed. Elsevier; Philadelphia, PA, USA: 2013. Chapter 11.
7. 55. Gratieri T., Kalia Y.N. Mathematical models to describe iontophoretic transport in vitro and in vivo and the effect of current application on the skin barrier. Adv. Drug Deliv. Rev. 2013;65:315–329. doi: 10.1016/j.addr.2012.04.012. [PubMed] [CrossRef] [Google Scholar]
8. 56. Li S.K., Zhang Y., Zhu H., Higuchi W.I., White H.S. Influence of asymmetric donor-receiver ion concentration upon transscleral iontophoretic transport. J. Pharm. Sci. 2005;94:847–860. doi: 10.1002/jps.20293. [PubMed] [CrossRef] [Google Scholar]
9. 57. Mudry B., Carrupt P.A., Guy R.H., Delgado-Charro M.B. Quantitative structure-permeation relationship for iontophoretic transport across the skin. J. Control. Release. 2007;122:165–172. doi: 10.1016/j.jconrel.2007.07.004.
10. Moscicka-Studzinska, A.; Kijenska, E.; Ciach, T. Electroosmotic flow as a result of buccal iontophoresis—Buccal mucosa properties. Eur. J. Pharm. Biopharm. 2009, 72, 595–599.
11. Ren, W.; Baig, A.; White, D.J.; Li, S.K. Characterization of cornified oral mucosa for iontophoretically enhanced delivery of chlorhexidine. Eur. J. Pharm. Biopharm. 2016, 99, 35–44.
12. Oliashirazi A., Wilson-Byrne T., Shuler F.D., Parvizi J. Patient-controlled fentanyl iontophoretic transdermal system improved postoperative mobility compared to intravenous patient-controlled analgesia morphine: A pooled analysis of randomized, controlled trials. Pain Pract. 2017;17:197–207. doi: 10.1111/papr.12432. [P ubMed] [CrossRef] [Google Scholar]
13. 36. Viscusi E.R., Ding L., Itri L.M. The efficacy and safety of the fentanyl iontophoretic transdermal system (IONSYS®) in the geriatric population: Results of a meta-analysis of phase III and IIIb trials. Drugs Aging. 2016;33:901–912. doi: 10.1007/s40266-016-0409-7.
14. Goldstein J. Sumatriptan iontophoretic transdermal system: A novel approach to migraine-specific therapy. Neurol. Clin. Pract. 2014;4:454–457. doi:10.1212/CPJ.0000000000000080. [PMC free article][PubMed] [CrossRef] [GScholar] oogle
15. 38. Tepper D.E. Sumatriptan iontophoretic patch for migraine. Headache. 2014;54:1563–1564. doi: 10.1111/head.12453.
16. Barben J., Ammann R.A., Metlagel A., Schoeni M.H., Swiss Paediatric Respiratory Research Group Conductivity determined by a new sweat analyzer compared with chloride concentrations for the diagnosis of cystic fibrosis. J. Pediatr. 2005;146:183–188. doi: 10.1016/j.jpeds.2004.08.085. [PubMed] [CrossRef] [Google Scholar]
17. 40. Hammond K.B., Turcios N.L., Gibson L.E. Clinical evaluation of the macroduct sweat collection system and conductivity analyzer in the diagnosis of cystic fibrosis. J. Pediatr. 1994;124:255–260. doi: 10.1016/S0022-3476(94)70314-0.
18. Brown C.D., Lauber C.A., Cappaert T. The effect of dexamethasone iontophoresis on decreasing pain and improving function in patients with musculoskeletal conditions. J. Sport Rehabil. 2015;24:327–331. doi: 10.1123/jsr.2014-0172.
19. Dixit N., Bali V., Baboota S., Ahuja A., Ali J. Iontophoresis—An approach for controlled drug delivery: A review. Curr. Drug Deliv.

2007;4:1–10. [PubMed] [Google Scholar]
20 42. Fischer G.A. Iontophoretic drug delivery using the iomed phoresor system. Expert Opin. Drug Deliv. 2005;2:391–403. doi: 10.1517/17425247.2.2.391
21. Syms C.A., 3rd, Grantham M.L. Otologic iontophoresis: A no-papoose technique. Ann. Otol. Rhinol. Laryngol. 2013;122:487–491. doi: 10.1177/000348941312200802. [P ubMed] [CrossRef] [Google Scholar]
22. 44. Comeau M., Brummett R. Anesthesia of the human tympanic membrane by iontophoresis of a local anesthetic. Laryngoscope. 1978;88:277–285. doi: 10.1288/00005537-197802000-00010.
23. Glass JM, Stephen RL, Jacobsen SC. The quality and distribution of radiolabelled dexamethasone delivered to tissues by iontophoresis. Int J Dermatol. 1979;19:519–515. http://dx.doi.org/10.1111/j.1365-4362.1980.tb00380.x.
24. Campisi, G.; Giannola, L.I.; Florena, A.M.; De Caro, V.; Schumacher, A.; Gottsche, T.; Paderni, C.; Wolff, A. Bioavailability in vivo of naltrexone following transbuccal administration by an electronically-controlled intraoral device: A trial on pigs. J. Control. Release 2010, 145, 214–220. [Google Scholar] [CrossRef] [PubMed]
25. Paderni, C.; Campisi, G.; Schumacher, A.; Gottsche, T.; Giannola, L.I.; De Caro, V.; Wolff, A. Controlled delivery of naltrexone by an intraoral device: In vivo study on human subjects. Int. J. Pharm. 2013, 452, 128–134
26. Comeau M., Brummett R., Vernon J. Local Anesthesia of the Ear by Iontophoresis. Arch Otolaryngol. 1973; 98(2):114-120. doi: 10.1001/archotol.1973.00780020120012
27. T Brusis, I Loennecken. Treatment of tinnitus with iontophoresis and local anesthesia. Laryngol Rhinol Otol (Stuttg). 1985 Jul;64(7):355-8.
28. J Russo Jr, A G Lipman, T J Comstock, B C Page, R L Stephen. Lidocaine anesthesia: comparison of iontophoresis, injection, and swabbing. Am J Hosp Pharm. 1980 Jun;37(6):843-7.
29. J. MICHAEL MALONEY, JOHN L. BEZZANT, ROBERT L. STEPHEN, TOMASZ J. PETELENZ. Iontophoretic Administration of Lidocaine Anesthesia in Office Practice. The Journal of Dermatologic Surgery and Oncology. 1992. 18 (11): 937-940. https://doi.org/10.1111/j.1524-4725.1992.tb02764.x
30. M A Ashburn 1, M Gauthier, G Love, S Basta, B Gaylord, K Kessler. Iontophoretic administration of 2% lidocaine HCl and 1:100,000 epinephrine in humans. Clin J Pain. 1997 Mar;13(1):22-6. doi: 10.1097/00002508-199703000-00005.
31. Sadler PJ, Thompson HM, Maslowski P, Liddle A, Rowbotham DJ. Iontophoretically applied lidocaine reduces pain on propofol injection. British Journal of Anaesthesia [Internet]. 1999;82(3):432–4. Available from: https://www.sciencedirect.com/science/article/pii/S000709121738618X
32. Galinkin, J. L., Rose, J. B., Harris, K., & Watcha, M. F. (2002). Lidocaine iontophoresis versus eutectic mixture of local anesthetics (EMLA) for IV placement in children. Anesthesia and analgesia, 94(6), . https://doi.org/10.1097/00000539-200206000-00020
33. Strout, T. D., Schultz, A. A., Baumann, M. R., Jordan, P. J., Worthing, B., & Burton, J. H. (2004). Reducing pain in ED patients during lumbar puncture: the efficacy and feasibility of iontophoresis, collaborative approach. Journal of emergency nursing, 30(5), 423–430. https://doi.org/10.1016/j.jen.2004.08.010
34. Petelenz, T., Axenti, I., Petelenz, T. J., Iwiński, J., & Dubel, S. (1984). Mini set for iontophoresis for topical analgesia before injection. International journal of clinical pharmacology, therapy, and toxicology, 22(3), 152–155.
35. Irsfeld, S., Klement, W., & Lipfert, P. (1993). Dermal anaesthesia: comparison of EMLA cream with iontophoretic local anaesthesia. British journal of anaesthesia, 71(3), 375–378. https://doi.org/10.1093/bja/71.3.375
36. Ikeda, H., & Suda, H. (2013). Facilitatory effect of AC-iontophoresis of lidocaine hydrochloride on the permeability of human enamel and dentine in extracted teeth. Archives of oral biology, 58(4), 341–347. https://doi.org/10.1016/j.archoralbio.2012.08.004
37. Cubayachi, C., Couto, R. O., de Gaitani, C. M., Pedrazzi, V., Freitas, O. d., & Lopez, R. F. (2015). Needle-free buccal anesthesia using iontophoresis and amino amide salts combined in a mucoadhesive formulation. Colloids and surfaces. B, Biointerfaces, 136, 1193–1201.
38. Thongkukiatkun W., Vongsavan K., Kraivaphan P., Rirattanapong P., Vongsavan N., Matthews B. Effects of the iontophoresis of lignocaine with epinephrine into exposed dentine on the sensitivity of the dentine in man. Arch. Oral Biol. 2015;60:1098–1103. doi: 10.1016/j.archoralbio.2015.04.006.
39. Smitayothin, T. L., Vongsavan, K., Rirattanapong, P., Kraivaphan, P., Vongsavan, N., & Matthews, B. (2015). The iontophoresis of lignocaine with epinephrine into carious dentine for pain control during cavity preparation in human molars. Archives of oral biology, 60(8), 1104–1108
40. do Couto, R. O., Cubayachi, C., Duarte, M., Lopez, R., Pedrazzi, V., De Gaitani, C. M., & de Freitas, O. (2021). Towards the advance of a novel iontophoretic patch for needle-free buccal anesthesia. Materials science & engineering. C, Materials for biological applications, 122, 111778.
41. Wallace, M. S., Ridgeway, B., Jun, E., Schulteis, G., Rabussay, D., & Zhang, L. (2001). Topical delivery of lidocaine in healthy volunteers by electroporation, electroincorporation, or iontophoresis: an evaluation of skin anesthesia. Regional anesthesia and pain medicine, 26(3), 229–238. https://doi.org/10.1053/rapm.2001.22633
42. Oshima, T., Kashiki, K., Toyooka, H., Masuda, A., & Amaha, K. (1994). Cutaneous iontophoretic application of condensed lidocaine. Canadian journal of anaesthesia = Journal canadien d'anesthesie, 41(8), 677–679. https://doi.org/10.1007/BF03015620
43. Glaviano, N. R., Selkow, N. M., Saliba, E., Hertel, J., & Saliba, S. (2011). No difference between doses in skin anesthesia after lidocaine delivered via iontophoresis. Journal of sport rehabilitation, 20(2), 187–197. https://doi.org/10.1123/jsr.20.2.187
44. Arapostathis KN, Dabarakis NN, Coolidge T, Tsirlis A, Kotsanos N. Comparison of acceptance, preference, and efficacy between jet injection INJEX and local infiltration anesthesia in 6 to 11 year old dental patients. Anesth Prog.2010;57(1):3-12.
45. Gratieri T, Kalaria D, Kalia YN. Non-invasive iontophoretic delivery of peptides and proteins across the skin. Expert Opinion on Drug Delivery 2011; 8(5):645–663.
46. Matthieu Roustit, Sophie Blaise, Jean-Luc Cracowski. Trials and tribulations of skin iontophoresis in therapeutics. BJCP. (2014). 77(1): 63-71. https://doi.org/10.1111/bcp.12128
47. Chinnapareddy, S. Novel Biomedical Approaches in Health Monitoring and Oral Care. Ph.D. Thesis, Clarkson Univeristy, Potsdam, NY, USA, 2012.
48. Matthieu Roustit, Sophie Blaise, Jean-Luc Cracowski. Trials and tribulations of skin iontophoresis in therapeutics. 2014; 77(1): 63-71. https://doi.org/10.1111/bcp.12128
49. Rirattanapong P., Vongsavan K., Kraivaphan P., Vongsavan N., Matthews B. Effect of the topical application of 50% lignocaine hydrochloride on the sensitivity of dentine in man. Arch. Oral Biol. 2013;58:1549–1555. doi: 10.1016/j.archoralbio.2013.06.003.
50. Saliba S.A., Teeter-Heyl C.L., McKeon P., Ingeroll C.D., Saliba E.N. Effect of duration and amplitude of direct current when lidocaine is delivered by iontophoresis. Pharmaceutics. 2011;3:923–931. doi: 10.3390/pharmaceutics3040923.