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Review Article

Innovations in existing routes and novel drug delivery systems for local anaesthetics

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ABSTRACT

New drug delivery systems (NDDS) are developed for improvement in efficacy of the drugs, provide maximum benefit to the patient and to minimize the adverse drug reactions. For local anaesthetics (LAs), the development of new effective delivery systems modulate the release rate, extend their anaesthetic effect , and helps to enhance their localisation as desired. The various routes of local anaesthetic delivery (epidural, peripheral, wound catheters, intra-nasal, intra-vesical, intra-articular, intra-osseous) are under innovation these days. Different methods such as include iontophoresis, electroporation, sonophoresis, and magnetophoresis are being used to enhance local anaesthetic permeation. Adjuvants are added to potentiate drug effects. The use of different delivery systems should help to keep the LA at the target site for longer periods prolonging the anesthetic or analgesic effect with an extended range of agents

Keywords: NDDS, Clinical techniques, Sonophoresis, Magnetophoresis, Micropolations

INTRODUCTION

Novel drug delivery system is defined as modifications of the existing systems or new systems developed to promote therapeutic effects and minimize the toxic effects of a drug by increasing the amount and persistence in the vicinity of a target cell.

Need for NDDS

- Improved patient compliance.
- Decreased ADRs.
- Increased efficacy.
- Ease of administration.
- Reduces dosage frequency.
- Cost reduction.
- Achieved by optimization of duration of action, controlling the site of release and maintaining constant drug levels

For local anaesthetics (LAs), new effective delivery systems intends to suitably modulate the release rate of these drugs, extend their anaesthetic effect, and enhance their localisation; this reduces problems of systemic toxicity. Local anaesthetics are the drugs which on topical application or local injection cause reversible loss of sensory perception, in limited area of the body. They can be classified into two groups, namely, amides (-NH-CO-) and esters (-O-CO-). The amide group is the most commonly used clinically; it includes longer acting like levobupivacaine, bupivacaine, dibucaine and ropivacaine

and intermediate acting like lignocaine, prilocaine, mepivacaine, articane.

Techniques

Local anesthetics can block almost every nerve between the peripheral nerve endings and the central nervous system. The most peripheral technique is topical anaesthesia to the skin or other body surface. Small and large peripheral nerves can be anesthetized individually (peripheral nerve block) or in anatomic nerve bundles (plexus anesthesia). Spinal anaesthesia and epidural anaesthesia merges into the central nervous system. Injection of local anaesthetics is often painful. A number of methods can be used to decrease this pain including buffering of the solution with bicarb and warming.[1]

Clinical techniques include

Surface anesthesia

Application of local anaesthetic spray, solution or cream to the skin or a mucous membrane. The effect is short lasting and is limited to the area of contact.

Infiltration anaesthesia

Injection of local anaesthetic into the tissue to be anaesthetized. Surface and infiltration anaesthesia are collectively topical anaesthesia.

Field block

Subcutaneous injection of a local anaesthetic in an area bordering on the field to be anaesthetized.

Peripheral nerve block

Injection of local anaesthetic in the vicinity of a peripheral nerve to anesthetize that nerve's area of innervation.

Plexus anaesthesia

Injection of local anesthetic in the vicinity of a nerve plexus, often inside a tissue compartment that limits the diffusion of the drug away from the intended site of action. The anaesthetic effect extends to the innervation areas of several or all nerves stemming from the plexus.

Epidural anaesthesia

A local anaesthetic is injected into the epidural space where it acts primarily on the spinal nerve roots. Depending on the site of injection and the volume injected, the anaesthetized area varies from limited areas of the abdomen or chest to large regions of the body.

Spinal anaesthesia

A local anaesthetic is injected into the cerebrospinal fluid, usually at the lumbar spine (in the lower back), where it acts on spinal nerve roots and part of the spinal cord. The resulting anaesthesia usually extends from the legs to the abdomen or chest.

Intravenous regional anaesthesia (Bier's block)

- Blood circulation of a limb is interrupted using a tourniquet (a device similar to a blood pressure cuff), then a large volume of local anaesthetic is injected into a peripheral vein. The drug fills the limb's venous system and diffuses into tissues where peripheral nerves and nerve endings are anesthetized. The anaesthetic effect is limited to the area that is excluded from blood circulation and resolves quickly once circulation is restored.
- Local anesthesia of body cavities (e.g. intrapleural anaesthesia, intra articular anaesthesia)
- Transincision (or Transwound) catheter anaesthesia, wherein a multilumen catheter is inserted through an insicion or wound and aligned across it on the inside as the incision or wound is closed, providing continuous administration of local anaesthetic along the incision or wound.[2]

Innovations in the already existing routes and novel routes of local anaesthetic delivery

Epidural

By this method patients can self-administer drug doses according to their analgesic needs. Here a staff-programmed pump and skilled and qualified members of the hospital staff is required. The use of epidural local anaesthetics is associated with a higher incidence of hypotension, motor block, and urinary retention, compared with use of opioids.[3] Trials have shown that administration of epidural local anaesthetics to patients undergoing laparotomy reduce gastrointestinal paralysis compared with systemic or epidural opioids, with comparable postoperative pain relief.[4] However, in a recent meta-analysis, only a continuous infusion of epidural local anaesthetics was superior to intravenous opioids in improving pain control and reducing adverse effects.[5] This method is being used during delivery, pain associated with cancer and pain in terminally ill patients.

Peripheral

It provides effective postoperative pain relief without systemic exposure to opioids. Using PCRA, small doses of local anaesthetics (ropivacaine, bupivacaine) is delivered via an indwelling catheter that can be placed in different regions of the body according to the surgery to be done. Infusions are controlled either by a staff-programmed electronic pump or by a disposable elastomeric pump.[5] An elastomeric pump is a device that

has a distensible bulb inside a protective bulb with a built-in filling port, delivery tube, and an antibacterial filter. Antibacterial filters are recommended with blocks involving a nerve plexus (and in neuraxial blocks). Analgesia can be delivered directly into a surgical incision (incisional PCRA), the intra-articular tissue (IA PCRA), or the perineural site (perineural PCRA) (Figure 1).[3]

Figure 1: Patients controlled perineural analgesia via infraclavicular brachial plexus catheter.

Wound catheters

Continuous infusions of local anaesthetics into the surgical wound at the end of the procedure via such cathetors (Figure 2). Continuous wound catheters can confer several benefits, including improved analgesia, reduced opioid use and adverse effects, increased patient satisfaction, and reduced hospital stay.[5]

Figure 2: Elastomeric pump for a wound catheter.

The use of continuous wound catheters consistently reduces the need for opioids (both rescue and total dose). Patients have consistently rated postoperative nausea and vomiting (PONV) as a primary concern after surgery.[6,7] The reduced need for opioids (though an infrequently measured result in randomised controlled trials) might contribute to increased patient satisfaction.[5] Reduced length of hospital stay has been associated with continuous wound catheters, especially in the cardiothoracic and orthopaedic surgery subgroups.5 Meta-analysis suggested the potential saving of one day of hospital stay.[5] Several reports have raised potential concern about wound infections from the presence of a catheter.[8]

Intranasal route

The nasal mucosa is an anatomical barrier, except for compounds with low molecular weight or highly lipophilic compounds. In case of nasal fractures, lignocaine and cocaine have been used in topical local anaesthesia in various forms like spray, paste or on cotton wool and pledgets. Compared to general anaesthesia it appears more safe and effective. A systematic review has found no significant differences between local anaesthesia and general anaesthesia as regards pain, cosmesis or nasal patency after nasal fracture manipulation performed under topical local anaesthesia.[9] A recent cochrane review showed that nasopharyngeal topical local anaesthetic or vasoconstrictor preparations prior to the use of a fibre-optic nasal endoscope did not demonstrate any advantages in using a topical treatment prior to endoscopy.[10]

Intravesical (bladder) route

The transport of local anaesthetics through the urothelium into deeper layers of the bladder has been increased significantly by electromotive drug administration.[11] It is a cost-effective way to deliver lignocaine with greatly improved penetration rate into the bladder wall.[12] Vehicles such as electromotive drug administration, new in situ delivery systems, and bioadhesive liposomes make it possible to extend intravesical therapy and drug administration to many bladder diseases.[11]

Intra-articular (IA) route

Arthroscopic surgery is associated with variable amount of postoperative pain. The intra-articular route of drug administration has a vital role in providing postoperative analgesia after the arthroscopic procedure. Samoladas et al. found that intra-articular ropivacaine is effective to reduce postoperative pain minimizing the use of systemic analgesia.[13] This study also stated that intra-articular injection of local anesthetic seems to provide an alternative and effective solution in pain control after knee arthroscopy. The use of intra-articular local anaesthetics is probably not advisable until the role of local anaesthetics in this regard has been clarified.

Intra-osseous route

Computer-controlled local anaesthetic delivery devices (C-CLAD) and systems for intra-osseous injection are important additions to the dental anaesthesia armamentarium.[14] C-CLAD using slow infusion rates can significantly reduce the discomfort of local anaesthetic infusions, especially in palatal tissues; C-CLAD facilitates palatal approaches to pulpal nerve block. It should find special use in cosmetic dentistry, periodontal therapy, and paediatric dentistry.[14]

Transdermal route of local anaesthetic drug delivery

Transdermal drug delivery is considered among one of the patient-compliant routes of drug administration. However, the stratum corneum, the outer most layer of the skin resists the penetration of drugs across the skin. Hydrophilic, ionised, and macromolecular substances are poorly permeable across the skin.[15] To enhance drug permeation in a passive manner, transdermal drugs should be lipophilic and should ideally have a molecular weight less than 500 Daltons.[13] Alternatively, by energy dependent active measures drug delivery across the skin can be enhanced. These include physical permeabilisation of skin or by driving the drug molecule across the skin. In addition to the use of eutectic mixture of local anaesthetics, and the use of controlled heat, other methods such as iontophoresis, electroporation, sonophoresis, and magnetophoresis can be used.[15]

Magnetophoresis

Magnetophoresis is a method of enhancement of drug permeation across the biological barriers by the application of a magnetic field (Figure 3). The predominant mechanism responsible for magnetically mediated drug permeation enhancement is known as "magnetokinesis".[13] The octanol/water partition coefficient of drugs increases when exposed to the magnetic field.[13] Magnetophoretic patch systems deliver drugs at a higher rate than nonmagnetic patch systems. In the rat model, the dermal bioavailability (area under the curve 0-6 hours) from the magnetophoretic patch system was significantly higher compared to a non-magnetic control patch.[13]

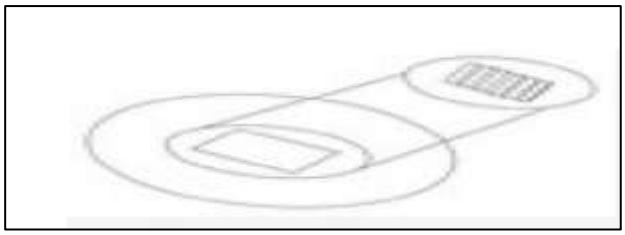

Figure 3: Magnetophoresis.

Sonophoresis/phonophoresis

The use of ultrasound for the delivery of drugs to, or through, the skin is commonly known as sonophoresis or phonophoresis (Figure 4). The frequency of the ultrasound wave corresponds to the number of times that the transducer tip is displaced per second of application time. High-frequency sonophoresis includes frequencies in the range of 0.7-16 MHz (most commonly 1-3 MHz).[16] Low-frequency sonophoresis includes frequencies in the range of 20-100 kHz and allows transdermal delivery of both hydrophilic and high-molecular mass permeants at therapeutic levels.[17]

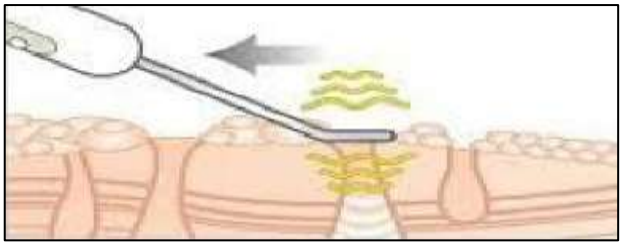

Figure 4: Sonophoresis.

The main contributor responsible for skin permeability enhancement by sonophoresis is acoustic cavitation. This causes the formation of acoustic microjets on the surface of the skin in a nonuniform manner.[17] When surfactant is included in the treatment of skin with low-frequency sonophoresis, a strong synergistic enhancement in skin permeability occurs, allowing delivery of hydrophilic permeants. Additionally, low-frequency sonophoresis-mediated transdermal delivery can be used to deliver macromolecules, including liposomes and nanoparticles.[17] This technology is currently approved for use by the federal drug administration (FDA) for local anaesthetics. In volunteers, a transducer has been used to administer an anaesthetic drug transdermally. When 0.5 MHz ultrasound in phonophoresis used for conduction anaesthesia with lignocaine hydrochloride, it was found to be more effective than the 1 MHz widely used in clinical situations.[18]

Microporation technologies

Skin microporation may be considered a minimally invasive technology that can be broadly divided into microneedle technology, thermal microporation, and laser ablation.[19] To improve the rate and extent of transdermal lignocaine across porcine ear skin, the application of novel laser microporation technology (painless laser epidermal system) has been used to create well-defined conduits in the skin.[20]

Electroporation

Electroporation is the application of short high voltage pulses that result in formation of transient aqueous pathways for diffusion of molecules across the skin.[15] In case of electroporation, the electrical pulses are applied only for fraction of a second; the interval between subsequent pulses allows the skin to depolarise.[15] Therefore, polarisation of skin does not interfere with the current flow or drug diffusion. In the porcine epidermis, the transport of lignocaine hydrochloride in case of low voltage electropulsation was found to be 8-fold more than the control.[15] The amount of lignocaine hydrochloride present in the epidermis was found to be 2-fold higher as well.

Electrokinesis (electrophoresis and or electro-osmosis) and permeabilisation of membranes are responsible for enhanced transdermal drug transport by low voltage

electroporation. The total duration of electrical current application during 20 minutes of low voltage electroporation is only one minute. Low voltage electroporation enhances drug permeation relatively more efficiently than constant direct current iontophoresis.[15]

Jet injection

In this technique a small amount of local anesthetic is propelled as a jet into the submucosa without the use of a hypodermic syringe/needle from a reservoir. This takes place when the knob is pressed to release air pressure which produces a fine jet of solution which penetrates the mucosa through a small puncture wound to produce surface anaesthesia. This technique is particularly effective for palatal injections.

Eutectic patches

A new topical local anaesthetic eutectic patch consisting of a mixture of lignocaine 70 mg and tetracaine 70 mg (Synera in the United States, Rapydan in Europe) has been developed.[21] This patch has an integrated heating element intended to enhance the flux of the tetracaine and lignocaine leading to more rapid and effective delivery of the local anaesthetics to the target area. The patch starts heating once removed from the pouch and exposed to atmospheric oxygen; it may increase skin temperature by up to 5°C.[21]

Dentipatch

A patch that contains 10-20% lidocaine is placed on the dried mucosa for 15 minutes. Hersh et al studied the efficacy of this patch and recommended it for use in achieving topical anesthesia for both maxilla and mandible.

Clinical

With the use of topical local anaesthetics for dermal laceration repair, a meta-analysis reviewed 22 trials with more than 3000 randomised patients; it concluded that topical tetracaine, bupivacaine, and lignocaine had an equivalent or superior analgesic efficacy to the intradermal infiltration of cocaine-containing anaesthetics. The topical preparations proved less expensive and were safer.[21,22] In another recent meta-analysis of 25 trials with more than 2000 subjects, three topical anaesthetics, (tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lignocaine) were found to be equally efficacious.[23] Tetracaine had the added advantage of a longer duration and was reported not to cause methemoglobinemia.[24] Another study has demonstrated that the lignocaine/tetracaine patch provided better local anaesthesia than the control at all application times under 60 minutes.[25]

Potential uses of topical anaesthetics include the following: for gaining pain-free vascular access; for skin or punch biopsies; for bone marrow aspiration; for treatment of postherpetic neuralgia; for immunisation; for myofascial pain due to trigger points; for nerve entrapment such as carpal tunnel syndrome; for regional block placement; and for dermal procedures requiring laser treatment.

Iontophoresis

Iontophoresis involves the active transportation of a drug into the skin using a constant low-voltage direct current. Ions migrate between electrodes of opposite charges, promoting ion transport through the skin (Figure 5).[26] A direct electrical current facilitates the dermal penetration of positively charged lignocaine molecules when placed under a positive electrode for local anaesthesia. Physicochemical properties, such as good aqueous solubility, and the presence of charged groups that render peptides and proteins "difficult to deliver" by other approaches, are ideal for iontophoresis.[27] The amount of drug delivered via iontophoresis is dependent on the current and the duration of delivery. The control afforded by constant current iontophoresis over transport rates means that peptide/protein delivery kinetics could mimic endogenous secretion profiles.[27] Moreover, complex input kinetics can be used to optimise and individualise therapy.

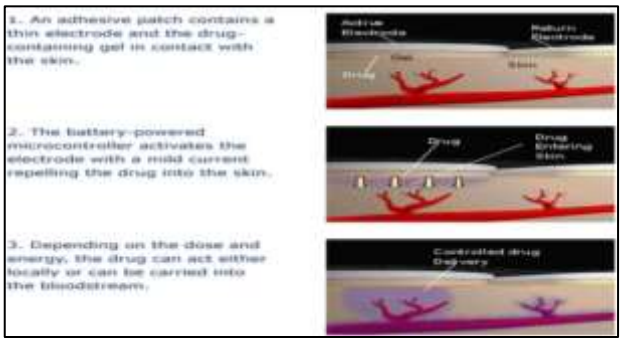

Figure 5: Iontophoresis.

Components of an anodal iontophoretic device are a current source; a current control device; anode (donor) reservoir system (with a positively charged drug/ion in solution); cathode reservoir system (on a different skin site). With an electric current, all cations move away from the anode and into the skin, and negatively charged ions move from the body into donor reservoir.

Iontophoresis has been known to cause skin irritation at higher current densities or upon longer application.[15,28,29] Moreover, when direct current electric field is applied over longer durations, an electrochemical polarisation occurs in the skin which decreases the magnitude of current flow through the skin.[15] This in turn could affect the amount of drug ions driven across the skin.

Small, portable iontophoresis devices have been developed. Dermal anaesthesia can be achieved fairly rapidly using lignocaine iontophoresis without needles.[26]

Adrenaline added to the lignocaine solution enhances the effect and duration of local anaesthesia during iontophoresis; this is due to the local vasoconstriction inhibiting lignocaine absorption into the systemic circulation.

Delivery can be hastened by using ultrasound. In a randomised controlled trial, ultrasound pre-treatment plus two-minute low-voltage iontophoresis provided better skin anaesthesia than sham-ultrasound plus two-minute low-voltage iontophoresis, and similar to standard, 10-minute high-voltage iontophoresis.[30] Lignocaine HCl 10% adrenaline 0.1% topical iontophoretic patch (LidoSite) is the first FDA-approved prefilled active anaesthetic patch. In volunteers, it was found that 2% lidocaine could be delivered up to 5 mm below the surface of the skin when the drug compound contained adrenaline, and when passive delivery occurred for at least 50 minutes after the active delivery has terminated.[31]

New drug delivery systems for local anaesthesia provide better analgesia and anaesthesia by altering the sensory component mainly. Efficacy and tolerability of drugs is improved by these novel methods.

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