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Prolonging the Block: Current Options

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ABSTRACT

Prolonged peripheral nerve blocks are desirable in several situations, and several methods are currently employed to achieve a prolonged sensory block. Additives added to single shot peripheral nerve blocks can cause modest prolongation of analgesia. continuous peripheral nerve blocks, even though costlier and technically difficult is the most effective way for prolonging the block for days. Newer formulation of local anesthetics and innovations in drug delivery systems also can help in increasing the duration of the analgesia for several hours.

Nerve blocks can provide effective analgesia in a variety of painful conditions, both acute and chronic. With the advent of ultrasound guided blocks, the success rates have improved and complications have been minimized. Prolonged blocks are desirable in several situations, and several methods are currently employed to achieve a prolonged sensory block. Apart from patient comfort, a prolonged nerve block allows us to decrease the dosages of systemic drugs like opioids and their side effects, mobilize the patient early and decrease the complications associated with prolonged immobilization, decrease pain induced cardiorespiratory effects, to name a few. This article discusses various methods to increase the duration of peripheral nerve blocks.

Factors Influencing the Duration of Peripheral Nerve Blocks

After injection at the target site, the local anesthetics are removed by various routes. They are distributed into the neighbouring structures

like muscles, fat and connective tissue. The more vascular the region more is the uptake into systemic circulation. For example,interpleural and intercostal nerve blocks are associated with the maximum systemic levels of local anesthetics. Traditionally it was thought protein binding influenced the duration of action, more protein bound drugs had a reservoir from which the drug can be releases thereby prolonging its action. However, there is no direct correlation with the degree of protein binding to the duration of action[1], as dissociation times of local anesthetics from Na+ channels are measured in seconds and do not have a bearing on the speed of recovery from the block.

The main factor determining the duration of the block is how long the drug stays near the nerve. Vascularity of the tissue, addition of vasoconstrictors and lipid solubility of the drug plays a major role. A dense block with a short acting agent can outlast a poor block by a long acting agent[2]. Currently bupivacaine ,levobupivacaine and ropivacaine are the most commonly used agents and they provide better sensory motor separation as compared to lignocaine. Analgesia lasting for days to weeks is desirable in a variety of conditions apart frompost operative state. They include chronic pain states like cancer-induced pain, complex regional pain syndrome or phantom limb pain.

Duration of a single injection peripheral nerve block(sPNB) depends upon the agent used and site of injection. For example, the average duration of sciatic nerve block with levobupivacaine, ropivacaine and bupicacaine is 1275,945 and 880 minutes respectively,[3,4]whereas it is around 890 minutes in a supraclavicular block with both levobupivacaine and bupivacaine.[5]

Additives to Prolong the Block

The most useful and clinically proven additive category to prolong drug nerve contact and thereby the duration of blockade is vasoconstrictors like adrenaline and phenylephrine. Opioids especially buprenorphine has been shown to prolong analgesia.[6] Clonidine and dexmeditomidine also can cause modest prolongation of analgesia in peripheral nerve blocks. Steroids like dexamethasone has been shown to prolong the duration of the block by few hours.[7]

Continuous Peripheral Nerve Blocks

Continuous peripheral nerve block (cPNB) is one of the widely used methods to provide prolonged analgesia.It involves placing a catheter near the plexus or the nerve under ultrasound and/or nerve stimulator guidance and continuous infusion of local anesthetic.In 1946, Ansbro[8]proposed the use of a continuous supraclavicular nerve block technique to prolong the duration of analgesia.Commonly used drugs are levobupivacaine, ropivacaine and bupivacaine. Rather than the concentration or speed of infusion, it is the total dosage of the drug that determines the effectiveness.[9]

The several advantages of cPNB include reducing additional analgesic requirements, decrease of postoperative joint inflammation and inflammatory markers, sleep disturbances and

opioid-related side effects, patient satisfaction and ambulation/functioning improvement, an accelerated resumption of passive joint range-of-motion, early discharge ,decrease in blood loss/blood transfusions, potential reduction of the incidence of postsurgical chronic pain and reduction of costs.[10,11]

Eventhough the effect of regional anaesthesiaas a whole in the overall outcome of patient's condition is still unclear, continuous peripheral regional anesthesia have been shown to improve functional outcomes after extremity surgery at least for a short term period (up to 6 months).[12,13]cPNB are being used to provide post op analgesia in day care cases and in the patients home after discharge.[14]It has been successfully used in children also.[15]

The main disadvantages of CPNB include difficulty in placing the catheter, need for expensive pumps,[16]intravascular migration,[17,18] inadvertent catheter removal,[19,20],infection,[21] catheter kinking and knotting,[22] block failure and vascular puncture and hematoma formation.[23]

Can Tachyphylaxis Happen in cPNB?

Tachyphylaxis, a form of acute tolerance can be seen with repeated administration of local anesthetics. However the key factor for development of tachyphylaxis is the timing of dose administration. If the second dose is administered before the first dose completely wears off, it can be avoided.[24]A loss of analgesia during cPNB should alert about other possibilities like catheter displacement of more serious problems like development of a compartment syndrome etc.

Drug Delivery Systems

Several novel drug delivery systems have been developed to provide prolonged nerve blocks. Various encapsulation matrices are being used and developed to act as a reservoir from which the drug can be released in a steady concentration. Vesicular carriers include liposomes,neosomes,transferosomes ,ethosomes and elastic deformable vesicles, they are used mainly for prolonged transdermal drug delivery.[25,26]Liposomes, cyclodextrins, microspheres are used as encapsulating agent for local anesthetic agents. Massive doses of local anesthetic can be enclosed in thesuitcase carrier encapsulating agent and delivered intactto the site of action.[27]

A common character of all encapsulation material is they are biodegradable with minimal tissue reaction and release the drug in a controlled fashion.Liposomes are lipid vesicles with a bilayer of phospholipids.They may be small unilamellar (SUV), large unilamellar(MUV) of multivesicular(MLV).[28] Lipid soluble drugs are loaded in the bilayer, water soluble drugs are incorporated in the aqueous compartment inside the bilayer. The biological activity of liposomes can be adjusted by varying the size of the liposome, the phospholipid composition, how the active drug is loaded, and the drug-to-lipid ratio.[16]

Liposomal Bupivacaine.

Liposomal bupivacaine has been approved by the FDA for wound infiltration after hemorrhoidectomy and bunionectomy.[29]It is available as a Depo-foam based lipid delivery system, (Exparel, PaciraPharmeuticals)where vesicles of Bupivacaine are loaded in aqueous chambers. It is a Multivesicularliposome(MVL), and consist of nonconcentric lipid bilayers. The release of drug from the MVL requires only a breach in the external layer, and release of a drug from internalvesicles leads to redistribution of the drug within the particle. The multivesicular structure makes the vesicles rearrange themselves without release of drug by internal fusion and division. [30] as of now, liposomal bupivacaine have been used in several surgical and orthopaedic procedures including mastectomy, hysterectomy, laminectomy, spinal cord fusion and also for transverse abdominal plane (TAP) block.[31] It is contraindicated in obstetric paracervical blocks, should not be mixed along with lignocaine, and not tested in age group less than 18 years. It should not be allowed to come in contact with antiseptics like as they may disrupt the lipid layers leading to uncontrolled release of bupivacaine.[32]

In a study on human volunteers, Davidson et al[33] noted that the peak plasma levels (C_{max})after a subcutaneous injection of 20 ml of 2% liposomal bupivacaine is comparable with that of a same volume of 0.5% bupivacaine,despite a 4 fold increase in the total dose in the liposomal preparation. The time taken to reach the peak levels were 7 fold more than the plain group. Thus it is possible to prolong the duration several times by administering more of the drug, and still keep C_{max}within safe limits. The duration of analgesia was increased upto 5 fold with liposomal preparation.

Liposomal encapsulated ropivacaine 0.5% has been tried for maxillary dental anesthesia, though no significant improvement in anesthetic efficacy was not seen.[34]Similarly,the same authors concluded that topical application of 2% liposomal ropivacaine was also not effective in decreasing pain of needle insertion in palatal mucosa.[35]

Liposphere encapsulated preparations are also being developed, the main advantages as compared to liposomes and microspheres include better physical stability,lowcost,ease of preparation, high dispersability in aqueous medium, controlled particle size and a more prolonged duration of action.[36] A novel ropivacaine lipid nanocapsules(LNC) has been developed and has shown increased dermal permeability in animal studies.[37]

The potential disadvantages of liposomes include a difficult manufacturing process where the drug might leak due to oxidation and hydrolysis,expensive, uncontrolled leakage of drug may occur following breakdown of the liposomes and some liposomal metabolites are neurotoxic.[38]

Other methods of encapsulation include micro and nanospheres, derived from co polymers of poly lactic and poly glycolic acid.(PLA or PLGA). Subcutaneous infiltration of biodegradable PLGA microparticles loaded with up to 2.5% bupivacaine–dexamethasone or 0.5% plain

bupivacaine was done in volunteers, Pain reduction was significantly better with the highest concentration bupivacaine–dexamethasone PLGA formulation in the period beyond 24 h up to 96 h.[39]

Hyaluronic Acid-Based Hydrogels Hyaluronic acid is anon-immunogenic naturally occurring mucopolysaccharide, used as a viscous carrier solution to prolong LA action. Cross linked hyaluronic acid has been shown to double the duration of action of bupivacaine.[40]Apart from this,Controlled-Release Local Anaesthetic Matrices are also available.An absorbable, controlled-release, local anaesthetic delivery system containing 16% (w/w) lignocaine (Xybrex) is capable of providing up to several days of reversible rat sciatic nerve block in a dose- (mass-) dependent fashion. [41]

Injectable Liquid Polymers.There are three types of polymers for encapsulation, namely, nondegradable synthetic polymers, natural biodegradables (that degrade to nontoxic products that are completely eliminated from the body), and drug-conjugated polymers (where a drug is attached to water-soluble polymer by a cleavable bond) Polymer-based formulations can be moulded to solid or paste like formulations according to the required type of dose, from injectable paste or liquid matrices to solid implants, only by choosing an appropriate molecular weight and polymer type.The use of a 15% bupivacaine lactic acid-*co*-castor oil copolymer prolonged the in vivo effect to 96-hour sensory block .[42]

Neurotoxins or biotoxins are an entirely new group of drugs thatare very potent and very specific blockers of the Na+ channel, and can be used to provide prolonged analgesia by local infiltration. Wound infiltration with neosaxitoxin after laparoscopic cholecystectomy provided lower pain scores after 12 hours as compared to bupivacaine, and no adverse events were more frequent in the neoSTX group.[43]

In conclusion, a prolonged sensory block has several advantages. Additives added to single shot peripheral nerve blocks can cause modest prolongation of analgesia. A continuous peripheral nerve block, even though costlier and technically difficult is the most effective way for prolonging the block for days. Newer formulation of local anesthetics and innovations in drug delivery systems also can help in increasing the duration of the analgesia for several hours. Currently they are approved only for local infiltration in specific surgeries. Further studies are needed before these new formulations are put into routine clinical use.

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