Peripheral Nerve Blocks in Patients with Diabetic Neuropathy and other Neuropathies: A Narrative Review

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ABSTRACT

Neuropathy, arising from different etiologies, can be a major debilitating condition that leads to pain,reduces physical movement and amputation. Among all known neuropathy etiologies, diabetes mellitus is one of the significant causes that results in peripheral and other type of neuropathies that result in physiological discomfort and mortality. Prolonged hyperglycemia-induced oxidative stress causes damage to neuron resulting in a range of symptoms to pain and internal organ failure. Although treatment strategies exist to alleviate the pain symptoms, there is no existing therapy to eliminate the root cause of neuropathy. Presently, peripheral nerve block by several anesthetic agents shows great promise in managing diabetes-induced neuropathy and neuropathies of other etiologies. This article discusses different types of neuropathies and their classifications with special emphasis on diabetic neuropathy. The following section discusses the extent of severity of the condition in terms of its epidemiology and associated complications. The article provides an elaborate idea on different anesthetic agents used in peripheral nerve block in diabetic neuropathy and other neuropathic conditions. Peripheral nerve block shows a potential efficiency when single and combination doses of anesthetics are used. Different adjuvants are also used in combination with anesthetics to prolong and enhance the effect of analgesia. Looking at the severity, physiological, psychosocial and economic burden of the neuropathic disease, more in-depth studies and discussion should be initiated to strengthen the use of peripheral nerve block in the management of diabetic and other neuropathies.

Keywords: Diabetic Neuropathy, Painful Neuropathy, Peripheral Nerve Block, Adjuvants, Sympathetic Nerve Block

INTRODUCTION

Peripheral neuropathy, commonly known as neuropathy, is an umbrella term for any kind of aberrant function of nerves of the peripheral nervous system (sensory, motor and autonomic nerve) arising due to varied etiology. Peripheral neuropathy can be inherited or can be acquired. Among the causes of acquired neuropathies, trauma, infection, medication, vascular disorders, vitamin imbalance, alcoholism, and systemic disorders are notable concerns. Among systemic disorders, renal dysfunctions, carcinoma, endocrine disorders and above all diabetes plays a crucial role in developing neuropathy. However, approximately 30-40% neuropathy is attributed to unknown etiology and known as idiopathic neuropathy.[1]

Out of all neuropathic etiology, diabetic neuropathy has the most detrimental outcome and difficult to manage. Over time, persistent hyperglycemia causes nerve damage after 5 years in 4% to 10% patients and after 20 yers in 15% patients. Diabetic neuropathy leads to symptoms ranging from pain and numbness in limbs to aberrant functions of internal organs involving cardiovascular, gastrointestinal, integumentary, and genitourinary system. Both pain management and surgical analgesia is a challenge in patients with diabetes mellitus.[1,2]

The present management options for diabetic polyneuropathy include stringent glycemic control and pain management by pharmacotherapy such as opioids, anticonvulsants, tricyclic antidepressants, selective serotonin, and noradrenaline reuptake inhibitors, anesthetic patches, etc. However, the management of pain in diabetic neuropathy still remains a challenge to clinicians as the current strategies are not satisfactory.[1,2]

An effective tool for analgesia in both Type 1 and Type 2 diabetic patients for perioperative management and pain control is peripheral nerve blocks. In the case of surgery, peripheral nerve block provides better and prolonged anesthesia than general anesthesia and also avoids the insulin-resistance and cardiopulmonary effects of general anesthesia.[3]

However, several factors to be kept on the note during the nerve block. Firstly, the factor of nerve toxicity by the used local anesthetic itself is a concern in diabetic and other preexisting neuropathy patients. Secondly, the dose adjustment of the anesthetic in connection with diabetes is an important consideration in peripheral nerve block by anesthetic agents. Finally, in patients with diabetes, the standard approach to localize peripheral nerve for injection may show a reduced efficacy.[4]

The following section will discuss the application of peripheral nerve block in diabetic patients and patients with other neuropathies. In this connection, the article will discuss the types of neuropathy, its epidemiology, and complication associated with it. In addition, it will discuss the existing treatment strategies and different agents and their combinations used for the treatment of neuropathies

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in special connection with the application of nerve block to diabetic neuropathy.

Neuropathy and its classification

The peripheral nervous system is mainly composed of different cell types that serve diverse motor, autonomic, and sensory functions of the body. Peripheral neuropathy is caused by the damage to the peripheral nerves other than brain and spinal cord. This problem can affect muscle movement, can impair normal sensation in the legs and arms, and cause pain.[5] Peripheral neuropathy may be classified as follows,

Hereditary Peripheral Neuropathy

Charcot-Marie-Tooth (CHT) disease is a group of neuropathies that are inherited from birth. This group of neuropathies are caused from mutations in more than 30 genes responsible in neuron formation.[6]

Chemotherapy-Induced Neuropathy

This is caused by various chemotherapeutic agents that are commonly used. This is the common side effect of these drugs. The dose-limiting side effect occurs in 30 to 40% of patients. Oxaliplatin, Carboplatin, and Cisplatin specifically induce a painful peripheral neuropathy but Suramin, Vincristine, and Paclitaxelinduce a mixed sensorimotor neuropathy.[7]

Entrapment Neuropathy

This occurs in nerves which is mechanically injured or significantly compressed at a specific location. The nerve injury may also results from compression osteoarthritis, acute trauma, or gout.[8]

Inflammatory Neuropathy (Guillain–Barré Syndrome)

This is an acute, demyelinating condition that results in polyneuropathy. This condition is characterized by diffuse ascending neuromuscular paralysis which may include autonomic nervous system, cranial nerve, and sensory nerve involvement.[9]

Postsurgical Inflammatory Neuropathy

It is an autoimmune or inflammatory process that can create severe postoperative neurologic problems. This type of neuropathy results as a immune response to different physiologic stress processes such as vaccination, infectious diseases, or a surgical procedure.[10]

Diabetic Polyneuropathy (Acquired Peripheral Neuropathy)

Diabetic neuropathy is mainly caused by Diabetes mellitus. In surgery patients with either known diabetes with uncontrolled hyperglycemia or in undiagnosed diabetes patients this is a common complication that prevails.[11]

Diabetic neuropathy

Epidemiology:

Epidemiologic study of diabetic neuropathy showed that in 13.3% diabetic patients suffers from neuropathic pain compared to 8.7% patients with impaired glucose tolerance, 4.2% patients with impaired fasting glucose, and 1.2% in control patients.[12] It is also reported that at 3years,the prevalence of neuropathic pain was 50%in diabetic patients, 49% in pre-diabetes subjects, and 29% in controls.[13] Another community-centered study conducted in diabetic patients (n=15,000) showed that almost 34% of patients had signs and symptoms of painful diabetic neuropathy, with an increased risk among type 2 diabetic patients, women, and South Asian population.[14]

The EURODIABIDDM complications study conducted among diabetic patients (n=3000), across 16 countries reported a 28% baseline prevalence of neuropathy. Moreover, it was also reported that in a 7 years span this gets increased by 23.5%.[15] Epidemiology of Diabetes Interventions and Complications (EDIC) study showed an initial 64% reduction in diabetic neuropathy risk in those on intensive compared to conventional treatment during the study period. In a follow-up study 30% risk reduction was reported.[16]

The prevalence rate of diabetic neuropathy in youth (aged below 20 years) with a shorter duration of diabetes has been reported. Data from patients with type 1 diabetes (n=1374) and patients with type 2 diabetes (n=258) were evaluated. This study showed presence of diabetic neuropathy in 7% type 1 and 22% of type 2 diabetic patients.[17]

According to an Indian study, a high prevalence (29.2%) of diabetic peripheral neuropathy observed among north Indian type 2 diabetes mellitus patients.[18] Whereas another study showed that the prevalence of diabetic peripheral neuropathy using the Michigan Neuropathy Screening Instrument (MNSI) history version and MNSI examination were found to be 18.3% and 32.2% respectively.[19]

Complication:

Diabetic neuropathy may create a series of serious complications like,

1. **Leg, foot or toe loss.** Nerve damage can cause foot sores and foot ulcers. The infection can spread to the bone resulting in ulcers and in severe cases may create gangrene. This may cause amputation of foot or toe or even lower leg.[20]
2. **Joint damage.** Instability, loss of sensation and joint swelling, joint deterioratation, and joint deformity may caused by nerve injury.[21]
3. **Urinary tract infections.** Nerve injury of bladder can cause urinary tract infections and incontinence.[22]
4. **Hypoglycemia:** Low blood sugar can cause sweating, shakiness, and a fast heartbeat.[23]
5. **Cardiovascular autonomic neuropathy:** Nerve damage that control blood flow can cause a sharp drop in pressure leading to dizziness and fainting.[24]
6. **Digestive complication:** Constipation or diarrhea can occur due to nerve damage. Diabetes-induced nerve damage can lead to a condition where the stomach empty rate is slow. Therefore, digestion impaired and both blood sugar level and nutrition of the body can be severely affected.[25]
7. **Sexual dysfunction:** Erectile dysfunction for male and difficulty with lubrication and arousal for female may occur.[26]
8. **Increased or decreased sweating:** Sweat glands can be disrupted by nerve damage causing excessive sweating, particularly while eating or night time.[27]

Treatment:

Studies showed that a number of drugs, used alone or in combination significantly reduces neuropathic pain. Therefore the treatments include,

Pathogenetic treatments

Glucose control: It is reported that intensive insulin therapy can reduce the incidence of neuropathy in type 1 diabetes patients.[28]

α-Lipoic acid: α-Lipoic acid is used to treat symptomatic diabetic neuropathy for it's antioxidant property.[29]

Symptomatic treatment

Several medical guidelines suggest serotonin–norepinephrine reuptake inhibitors, tricyclic agents, GABA analogues as first-line treatment followed by opioids and topical treatments.[30]

Tricyclic agents: Tricyclic agents like Amitriptyline, Desipramine and Imipramine showed an efficacious result in diabetic neuropathy treatment.[3]

Serotonin–norepinephrine reuptake inhibitors: Duloxetine and Venlafaxine act by blocking of serotonin and noradrenaline reuptake are used for diabetic neuropathy treatment.[31]

Carboxamides, GABA analogs and other historical Anticonvulsants: Carbamazepine, Oxcarbazepine[32] and Gabapentin[30] are the commonly used drugs. Pregabalin showed potent efficacy and widely used for diabetic neuropathy.[33] Topiramate was shown to be potent in symptomatic treatment of neuropathic pain in diabetic neuropathy.[34]

N-methyl-D-aspartate receptor antagonist: Dextromethorphan has been found to be effective when used on its own or in combination with quinidine.[35]

Opioid analgesia: Tapentadol showed potent action for neuropathic pain treatment.[36] There are many other opioids such as Melanocortins, Enkephalins, Nociceptin/orphaninFQ,enkephalins, dynorphins, and endorphins show good analgesic effect in managing neuropathic pain.[37]

Other treatments

Capsaicin topical application, 0.1% topical clonidine gel, isosorbide dinitrate spray, 5% lidocainepatches and botulinum toxin type A has been used for pain reduction in diabetic neuropathy.[3]

Peripheral nerve block as a treatment

Peripheral nerve blocks are commonly defined as the injection of neurolytic agents or local anesthetics that are used directly into or near to the peripheral nerves. These injections results in the temporary blockage of nerve impulse conduction in the peripheral nerves. The nerve blocker can either be single dose injection which is the one time injection of anesthetic dose to the targeted nerve for perioperative analgesia or surgical anesthesia or continuous injection which means percutaneous insertion of a catheter directly near to the targeted peripheral nerve. The continuous injection is to give sustained nerve block by continuous local anesthetic infusion for postoperative analgesia.[38]

Inflammation, oxidative stress, and mitochondrial dysfunction induced by long-standing hyperglycemia result in insufficient blood vessel function around the nerve, and changes in sodium and calcium channel expression.[11] Hence Local anesthetic drugs, like lidocaine, bind at a residues composed site in the internal pore region of the sodium channel and block the peripheral nerve.[39]

As neuropathic nerves are more potent to local anesthetics, the potency of nerve block would be higher in diabetic peripheral neuropathy patients. A retrospective study in patients receiving supraclavicular nerve blocks showed that the success rate was higher in diabetic patients than in non-diabetics (96% in diabetes mellitus vs. 87%), irrespective of sex or BMI.[40]

Peripheral nerve block agents

There are number of peripheral nerve block agents like

Lidocaine

Lidocaine is a widely used local anesthetic (LA) for nerve block in peripheral diabetic neuropathy.[41] Therefore lidocaine induced sciatic nerve block duration had been studied by using Zucker diabetic fatty rats (early diabetic) or 18 weeks (late diabetic), and age-matched healthy control rats. 0.2 ml lidocaine 2% was used to block the nerve. Whereas, early diabetic animals didn't report increased signs of nerve dysfunction after lidocaine induced nerve block but late diabetic rats receiving insulin showed intermediate results.[42]

Ropivacaine

Ropivacaine is a long-acting amide local anesthetic agent to reversibly inhibit the nerve impulses, thus causing a sustained sensory or motor blockade suitable for acute pain relief in diabetic neuropathy.[43]

A study showed the prolonged effect of Ropivacaine as a peripheral nerve-blocking agent in diabetic compared with non-diabetic patients. The prospective study included type 2 diabetes patients with minor nerve injury and non-diabetic patients. A sub-gluteal sciatic nerve block (4.75 mg/ml of 20 ml ropivacaine) was performed with an ultrasound application coupled with nerve stimulation process. The study reported that hemoglobin and creatinine values were higher in the diabetic patients significantly. The study also reported that the median duration of the sensory block and the motor block were higher in the diabetic group.[44]

On the other hand, the study showed that magnesium increased the sensory block duration compared to ropivacaine (0.25%). In comparison with evoked pain score in the group of ropivacaine alone (0.375%), ropivacaine plus magnesium (0.25%) showed a higher efficacy in relieving pain at 6 hours.[45]

Bupivacaine

Bupivacaine (0.5%) has been used for low action anesthesic agent by peripheral nerve blockade. However, a series of case studies reported that a combined femoral and sciatic nerve block using 0.25% bupivacaine may be an appropriate and safe anesthetic process for surgery.[46]

Mepivacaine

A short-acting local anesthetic like Mepivacaine is also used in axillary nerve blocks in diabetic neuropathy. In

this study,an ultrasound approach combined with nerve stimulation like an axillary nerve block (20 mL mepivacaine of 15 mg./mL concentration) was performed. The result reported that the average sensory block time duration was similar between diabetic neuropathy vs. healthy patient (235±52 vs. 230±54 min,).[47]

Adjuvants used in peripheral nerve block in neuropathy

Epinephrine

Epinephrine is used to prolong the duration and block systemic reabsorption of local anesthetics. Lidocaine with epinephrine ((high-dose) for axillary block increased motor and sensory nerve block timing by25 and 40 minutes.[48]

Clonidine

Clonidine is an alpha-2 agonist having the ability to prolong nerve blockade. It was shown that with bupivacaine itincreases the popliteal sciatic nerve block by almost 3–4 hours.[49]

Dexmedetomidine

Dexmedetomidine (alpha-2 agonist) having almost 7 times higher potency than that of clonidine. Several studies have reported that Dexmedetomidine with bupivacaine increases the nerve block by almost 8 hours and with ropivacaine increases the duration of the blocks by almost 4 hours.[50,51]

Dexamethasone

Dexamethasone with long-acting local anesthetics can increase the nerve blockade from 730 to 1306 minutes. In addition,when used with intermediate-acting anesthetics it increases the nerve blockade from 168 to 343 minutes.[52]

Tramadol

Tramadol, a weak central-acting opioid have Sodium and potassium channel blocking properties and can block motor and nociceptive function.[53,54]

Magnesium

Magnesium (N-Methyl-D-aspartate antagonist) acts to moderate calcium influx into neurons.[55] Magnesium significantly prolongs peripheral nerve block, when added with Bupivacaine, Prilocaine,and Levobupivacaine.[56]

Combination therapy

Several studies showed that Peripheral nerve block agents can be more potent and efficacious when used in various combination.

Lidocaine and bupivacaine

Studie shave shown that diabetis mellitus patients with neuropathy generally have longer block duration compared with non-diabetic patients without neuropathy in blocking the sensation of the popliteal sciatic nerve.[57]

Another study reported that ultrasound-guided popliteal sciatic nerve block with a 1:1 mixture of lidocaine (1%) and bupivacaine (0.5%) have shown different results for diabetic peripheral neuropathy patients. The patients had a time ratio of 1.57 thus 59% short time duration to onset of sensory blockade observed. Thus the study concluded that, after an ultrasound-approached popliteal sciatic nerve block, diabetic peripheral neuropathy patients reported reduced time to onset of sensory blockade, when compared with patients without neuropathy.[57]

Lidocaine alone or with adjuvants and ropivacaine

A recent study reported that after administration of anesthetics like 1% lidocaine alone, or anesthetics with adjuvants like ropivacaine 0.5% solution alone, lidocaine 1% solution with clonidine (7.5 mg/ml), or lidocaine 1% solution with epinephrine (5 mg/ml), increases the duration of sciatic nerve block in diabetic rats. Whereas with ropivacaine (0.5%) alone the duration of the sciatic nerve block was significantly higher in diabetic rats.[58]

Prilocaine and of Levobupivacaine

Poorly regulated blood glucose results in a higher risk of nerve or micro-vascular damage. Therefore a combination of the peripheral blocking agent can explain the theory by a prospective study. Researchers divided a cohort of 48 diabetic patients into three groups based on their glycosylated hemoglobin (HbA1c) (5–6%, 7–8%, 9–10%). The study suggested that the regression time of both motor block as well as the sensory block was significantly longer in the group with the highest HbA1c. A standardized local anesthetic mixture containing Prilocaine and Levobupivacaine was used in the study. The study concluded that the regression time of the sensory block was longer in patients with poor glycemic control than in patients with better glycemic control.[59]

Limitation of peripheral nerve block

Although peripheral nerve block is having potent efficacy in diabetic neuropathy, the blocking agents have certain limitations like,

Nerve toxicity

Diabetic neuropathy is a metabolic strain on a peripheral nerve that is aggravated by regional anesthesia.[60] It was reported that with 4% lidocaine, diabetic nerves showed more signs of damage than control nerves. A study suggested different combinations of local anesthetics on histologic changes in diabetic or non-diabetic rats. There was more nerve damage in diabetics receiving a lidocaine/clonidine combination, or ropivacaine, as compared with 1% lidocaine.[58] Therefore another study reported no clinically significant increase in neurotoxicity with lidocaine in diabetic fatty (ZDF) rats.[42]

Therefore, a review of case reports and studies in diabetics considering nerve damage after local anesthetics reported only six case reports on new-onset nerve damage after regional anesthesia in diabetics.[61]

Infection

The risk of infection increases over time with a peripheral nerve block. Study concluded diabetes and postoperative hyperglycemia to be risk factors for infection after perineural catheter placement.[62] Another study evaluated 747 cases of ultrasound-guided peripheral nerve blocks and found that although bacterial colonization and catheter infection are low (10 and 0.13%), a significant association between bacterial catheter colonization and diabetes observed.[63]

CONCLUSION

In light of the above discussion, it is evident that given the

limitation of exisiting therapeutic strategies for neuropathies, peripheral nerve block has been established as an intriguing option for pain management especially in diabetic neuropathy. However, more large scale controlled trials and other relevant studies are warranted to further bolster the potency of nerve block in managing neuropathic pain. In addition, search for newer and safer anesthetic agents and adjuvants is also the need of the hour. The target remains to prolong and enhance the effect of anesthesia and to reduce the adverse outcome of peripheral nerve block.

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