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REVIEW ARTICLE

The Evolution of Peripheral Nerve Treatment for Trigeminal Neuralgia - Peripheral Injections

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ABSTRAK

Kesakitan yang teruk melibatkan kawasan yang disarafi oleh cabang saraf deria rasa muka, terutamanya pada golongan wanita berusia merupakan ciri utama neuralgia trigeminal. Diagnosis keadaan ini biasanya boleh ditentukan berdasarkan tanda dan gejala klinikal. Penerbitan sebelum ini telah mendedahkan bahawa terdapat dua cara utama dalam rawatan neuralgia trigeminal iaitu rawatan perubatan dan pembedahan. Rawatan perubatan melibatkan pengambilan sistemik pelbagai jenis ubat atau aplikasi setempat pelbagai jenis bahan. Pengenalan ubat anti-konvulsif semasa Perang Dunia Kedua telah mengubah kaedah rawatan dan seterusnya menjadikan ia rawatan utama bagi neuralgia trigeminal. Walau bagaimanapun, manfaat ubat ini tidak berkekalan. Ulasan ini meringkaskan evolusi suntikan saraf periferi dalam rawatan neuralgia trigeminal sepanjang 150 tahun yang lalu.

Kata kunci: neuralgia trigeminal, suntikan alkohol, suntikan glycerol periferi, suntikan bius setempat, suntikan botulinum toxin

ABSTRACT

Trigeminal neuralgia presents as a characteristic severe painful condition that usually afflicts the area(s) innervated by the branches of the facial sensory nerves, especially the elderly females. The diagnosis can usually be made based solely on the presenting clinical signs and symptoms. Early literatures had revealed that there have always been two major means of treatment for trigeminal neuralgia; medical and surgical. Medical treatments involved systemic intake of various drugs or the topical applications of many different materials, not forgetting that bleeding and purging has been tried in the past. The introduction of anti-convulsants during the

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second World War had changed completely the way this painful condition was treated as this therapy later become the mainstay treatment for trigeminal neuralgia. Their beneficial effects, however may not be long lasting. This review summarises the evolution of peripheral nerve injection as a treatment for trigeminal neuralgia over the last 150 years.

Keywords: trigeminal neuralgia, alcohol injection, peripheral glycerol injection, local anaesthetic injection, botulinum toxin injection

INTRODUCTION

Trigeminal neuralgia (TN) or tic douloureux is a sudden, severe brief stabbing recurrent pain in one or more divisions of the trigeminal nerve (CN V) (Merskey & Bogduk 1994). The diagnosis of TN can be made solely based upon identification of clinical signs and symptoms like typical severe painful condition not seen in other conditions, and the fact that it commonly affects the elderly women. The earliest descriptions of TN were often too vague and were classified under the broad spectrum of head ailments/"kephalalgia" such as Hippocrates' "infinite forms" of headaches, Galen's "heterocrania", or Aretaeus's "hemicrania".

According to Lewy, the first authentic case of trigeminal neuralgia was recorded by Bretschneider in 1847 (Lewy 1938). Suffering from TN himself for 4 years, Johannes Laurentis Bausch, a well-known physician in Germany, was the first to provide a clear description of the pain which had prevented him from eating, speaking, and led eventually to emaciation and a stroke that killed him in 1665. Following that, John Locke as a famous English philosopher and physician had provided a full description of TN including its management while treating the Countess of Northumberland, wife of the English ambassador to France, who suffered from excruciating right-sided facial pain which failed to relieve with two teeth extraction. TN became a definite clinical entity perceived as an illness of convulsion under French surgeon Nicolaus Andre and was designated "tic douloureux" which implied facial spasm accompanied by violent and intolerable pain. After that, English physician, John Fothergill wrote of what he called a newly described condition in which the pain at time was sudden and excruciating, lasting a short time, returning at irregular intervals, affecting people of advanced age, women more than men, and what he suspected to be related to tumours. In 1782, Thouret reported that TN predominantly occurred in nerves of the face particularly the infraorbital nerve. In 1802, different variants of tic douloureux had been classified by Chaussier according to the division of trigeminal nerve including the facial nerve. It was Samuel Fothergill who detailed the classification of the site of disease as Vth nerve. However, the TN

was finally considered as a localized condition to trigeminal nerve after the findings of Charles Bell at late 1820s, where he classified the Vth and VIIth nerve with their specific functions (Eboli et al. 2009).

Early literatures had classified the treatment modalities for TN into medical and surgical management (Cherrick 1972). The medical management available in the past included topical application of moisturizer cream, vesicants, heat, opiates, counterirritants for example, plasters and blisterings, leeches, bleeding and purging (Cherrick 1972). In the early nineteenth-century, the preferred medication for TN included quinine sulfate, hemlock, ferrous carbonate, ether, arsenic in gruel and camphorated mercurial ointment. After that century, newer medications like vitamin B and liver extracts, intravenous histamines, vasodilators, mephenesin carbamate, chlorpromazine and cobra venom were added on to the list (Cherrick 1972). During the First World War, trichloroethylene was reported to cause facial numbness in workers in German plants. After the war, it was tested as a medical therapy by having patients inhaling it. However, the treatment had yielded variable success rate (Glasser 1931). These large arrays of treatment show our limited understanding on the treatment of TN until the introduction of anticonvulsants.

Since then, medical management especially with the prescription of anticonvulsants (carbamazepine, dilantin sodium, baclofen, lamotrigine and oxcarbazepine) has become the mainstay treatment for TN. The first introduced anticonvulsant was diphenylhydantoin sodium (dilantin), which was reported as an effective pharmacological therapy in 1942 (Bergouignan 1942). This was followed by the introduction of carbamazepine two decades later (Blom 1962). Carbamazepine act as sodium channel stabilizer which prevent the repetitively and sustained firing in abnormal afferents by preferentially biding to the voltage-gated sodium channel. It was the most widely studied medication and remains the preferred choice of drug in treating TN currently (Jorns & Zakrzewska 2007). Study showed carbamazepine as an effective long-term management in 69% of patients whom the medication was initially effective (Taylor et al. 1981). Carbamazepine can be replaced with oxcarbazepine in the event of poorly acceptable adverse effects (Zakrzewska 2019). The second generation of anticonvulsants (baclofen, gabapentin, pregabalin, lamotrigine, clonazepam, phenytoin, sodium valproate or opiates) can be considered when patient suffer from persistent neuralgia despite achieving therapeutic blood level of carbamazepine (Jorns & Zakrzewska 2007). Carbamazepine and other anticonvulsants unfortunately are not miraculous drugs that are always effective in all TN patients as their positive effects might not be long lasting (Zakrzewska 2019). The long-term efficacy of carbamazepine up to initial success in 60% of participants has been reported in a study evaluating of 146 patients over a 16-years period.

Carbamazepine was only found to be effective in 22% of participants after 5 to 16 years later while 44% required additional or adjunct therapies (Taylor et al. 1981). In such a situation, surgical treatments may become unavoidable.

Surgical management is a good alternative treatment for those who have failed to response to the medical treatment or severely affected by their adverse effects (Meirowsky & Pipito 1943; Bagheri et al. 2004). A study was reported that up to 44% of TN patients ended up in this treatment category (Taylor et al. 1981). In fact, prior to the introduction of anticonvulsants, the success of securing remission from surgical intervention was higher than medical therapy. The two important targets for surgical intervention include the peripheral nerve branch and the Gasserian ganglion. Peripheral procedure including nerve ablation using injection of neurolytic chemical agents, surgery, radiofrequency thermocoagulation of the nerve peripherally and cryotherapy. Peripheral nerve surgery included neurotomy, neurectomy, extraction of the nerve and nerve stretching (Fields 1996). Surgery involving the Gasserian ganglion at the central nervous system includes resection, rhizotomies via thermal (pulsed radiofrequency thermocoagulation), microvascular decompression and stereotactic gamma knife radiosurgery (Bagheri et al. 2004; Yadav et al. 2015). This manuscript will review the evolution of peripheral surgical management for trigeminal neuralgia in two parts. The first part of this series reviews how the use of peripheral injectable chemicals such as alcohol, glycerol, local anaesthesia, streptomycin or botox had evolved over time in the management of trigeminal neuralgia. The second part of this series looks into surgical interventions such as peripheral neurectomy, cryotherapy and other newer experimental form of peripheral treatment currently available for trigeminal neuralgia.

PERIPHERAL INJECTIONS

Peripheral injection of different chemical agents into or around the affected nerve has been practiced since the turn of the last century. The initial aim then was to fix the affected nerve. Nowadays, the main aim of peripheral injection is to prevent the stimulation of abnormal conduction pathways by interfering with the afferent pathways using various chemical substances. The first substance used were chloroform by Bartholow in 1874 and followed closely by osmic acid by Billroth & Neuber in 1884 (Cushing 1920). However, their duration of action was too restrictive as their injections were given at the superficial foramina of the peripheral nerves. These agents were later abandoned. Later on, boiling water, alcohol, glycerol, phenol, tetracaine, and streptomycin were included into this armamentarium with some success (Mckenzie 1925; Shah et al. 2011).

It is well acknowledged that with peripheral injections of chemical substances, pain relief is not permanent, despite its recognizable advantage. Peripheral chemical injection particularly

alcohol injection allows patients to experience transient anaesthetic effect compared to permanent numbness after neurosurgical procedures such as microvascular decompression. Studies have been reported several patients were intolerable to the effect of permanent numbness and this is great alternative option for them to experience the effect reversibly (Sweet 1950, McLeod & Patton 2007). stated that such injection will also accord pain relief for debilitated patients who would then become able to consume food to restore their health (Sweet 1950).

Alcohol Injections

Injection to the peripheral branches of trigeminal neuralgia using alcohol has started since early 20th century (Lockwood 1909; Shirres 1912). In 1901-1902, Abadie and Verger were reported to provide injection of cocaine subcutaneously followed by alcohol into the affected area of TN (Harris 1951). Schlosser and Matas have been cited as the first persons to describe their method of alcohol injection in 1903 (Crich 1938). Since then, the injection technique has been simplified and improved by Ostwald (1906), Schlosser (1907), Levy and Badoin (1906), Hauck (1906), Patrick (1907), Hecht (1907), Kiliani (1907), Harris (1912), Hartel (1912) and Penman (1949) (Harris 1951). Two different injection techniques were introduced to deliver the peripheral alcohol injection. The first injection technique was performed through transcutaneous towards the base of skull at the foramen ovale or foramen rotundum (Cushing 1920). The second injection technique aimed more distally to the nerve passing recognizable foramina in the facial area. Alcohol injection can be performed easily but blindly using 0.5-2.0 ml of 80-100% alcohol. Mckenzie (1925) described that the only true guide was to hit the nerve with the needle to produce the classic spasm of radiating pain. However, it is hard to control the spread of chemical agent within a closed space, with risk of spread to the subarachnoid space being a possible complication (Cushing 1920). Patrick reported only 18% success rate was achieved at first attempt of deep injection of alcohol due to the difficulty to locate precisely the intended anatomical landmarks (Patrick 1912). Nevertheless, reported pain relief last for a mean of 6-17 months were achieved in both deep and peripheral alcohol injection (Bagheri et al. 2004; Mckenzie 1925; Oturai et al. 1996; Grantham & Segerberg 1952), but with 10-39% failure rate (Grantham & Segerberg 1952; Peet & Schneider 1952; Ruge et al. 1958; Quinn 1965; Fardy et al. 1994). Fardy et al. (1994) reported a longer pain-free period of 19 months for the inferior alveolar nerve block in comparison to 13 months observed for the infraorbital nerve block. However, a substantially longer duration of pain relief can be achieved with multiple blocks of the same nerve. Han et al. (2017) reported that pain relief was achieved for 39 months with alcohol injection given through the foramen ovale into the Gasserian ganglion, blocking the mandibular branch as

well as peripheral branches following successful injections. Most studies revealed that the effective period of alcohol injection will shorten with the subsequent injections (Shah et al. 2011; Markham 1973). Nevertheless, the study by McLeod and Patton showed that repeated alcohol injections did not suffer any significant fall in the duration of pain relief for up to 14 injections of nerve block (McLeod & Patton 2007).

Meanwhile, a case of trigeminal neuralgia reported by Mckenzie showed that increased pain relief period was possible following a re-injection (Mckenzie 1925). His patient was reported to be pain free for 9 months during the first injection. This duration increased to 14 months upon re-injection-despite the fact that the patient received a deep alcohol injection. Repeated injections have been reported to neither cause adverse effect to patients nor affect the outcome of subsequent treatments such as microvascular decompression (McLeod & Patton 2007).

However, the deep injection of the Gasserian ganglion through the foramen ovale has been reported to cause alcohol to enter the subarachnoid space. Mckenzie (1925) cited a case of a complete paralysis of almost all the cranial nerves being observed because of this accidental spread. In another case report, Cushing described attending to a female patient who had endured extreme vertigo six months after ganglion injection, so much so that she could not hold up her head (Cushing 1920). In addition, severe eye lesions were apparently frequent (Cushing 1920; Mckenzie 1925). The mortality of this procedure, however, was low, at less than 1% in experienced hands (Cushing 1920). To minimize causing these complications, Sweet as far back as 1950 began taking radiographs to ascertain the position of the needle prior to injection (Sweet 1950).

Several other severe complications have also been associated with peripheral alcohol injections. In 1973, Markham (1973) reported an abrupt loss of vision in a patient subsequent to infraorbital nerve block using alcohol. It was speculated that the injected alcohol had penetrated the orbit and result in the spasm of central retinal artery. When treating TN of the mandibular branch, extra-oral injection of the mandibular nerve has been reported to cause necrosis of the ipsilateral premaxillary side of skin, mucosa and bone of hard palate (Richardson & Straka 1973). Another devastating adverse effect was reported in a case of alcohol block injection to the maxillary nerve in the left pterygo-palatine fossa through the sigmoid notch. Although pain was relieved, the patient subsequently developed ankyloses due to possible iatrogenic alcoholic destruction of the temporomandibular joint. The patient required condylectomy to improve mouth opening and to remove the partial denture stuck inside the mouth (Phillips & Whitlock 1976). Having resemblance to Sweet, Littler in the 1980s undertook radiographic-guided administration of alcohol to provide better control of the peripheral injection (Littler 1984). More recently, other radiographic-guided methods

of deep alcohol injection such as ultrasound-guided and fluoroscopy-guided approaches had improved the accuracy of needle insertion to the desired location for alcohol injection (Han et al. 2017). In addition, aspiration prior to injection is also helpful to ensure that no alcohol is injected into the vascular system (Shah et al. 2011).

Other complications that have been reported following alcohol injection include non-neuralgic pain or sometime excruciating pain post injection, swelling, burning sensation, dysaesthesia, fainting, transient oedema, haematoma, diplopia, and bone necrosis (Shah et al. 2011; Fardy et al. 1994). It has been suggested that local anaesthetic agents should be added to alcohol injections as a high concentration of local anaesthetics around the nerve would minimize hyperesthesia and dysaesthesia following injection (Masuda 2001).

Even though there is a remarkable list of adverse effects associated with this method of treatment, peripheral alcohol injection has survived the onslaught of medical advancement and remains a mode of treatment in some less developed countries or for the elder and/or medically compromised patients or, for those refractory patients with drug-resistant trigeminal neuralgia or unwilling to undergo neurosurgical procedures (Shah et al. 2011; Han et al. 2017; Tiwari et al. 2019). Deep injection of alcohol, however, has fallen out of favour due to advancement in neurosurgery.

Peripheral Glycerol Injections (PGI)

The discovery of glycerol use for trigeminal neuralgia patients was an accidental finding in 1970s when it was utilized as a vehicle for tantalum powder marker to identify the retroganglionic cistern for subsequent stereotactic calculation. By merely injecting this mixture, researchers discovered paroxysmal pain relief prior to the performance of gamma knife procedure (Leksell 1971). The earliest use of glycerol in the treatment of TN was pioneered by Håkanson in 1981 when it was shown to provide pain relief when injected into the trigeminal cistern (Håkanson 1981). Current PGI is a modification of the technique aiming at the peripheral branches of trigeminal nerve that was introduced by Stajčić in 1989. This treatment involves slow injection of sterile 99.9% anhydrous glycerol at the foramen of the affected trigeminal branches, 30 minutes after the administration of local anaesthesia. In comparison to absolute alcohol, the higher viscosity of glycerol made it difficult to administer, but is less painful than the alcohol injection. In Stajčić's study, thirteen patients with 17 affected nerves underwent PGI. A pain-free period between 6 to 26 months was recorded for 12 nerves. Pain recurred in slightly more than one-third of nerves 3-18 months following treatment. Subsequent PGI successfully provided pain relief for half of these nerves. It was concluded that this minimally invasive procedure could produce results as effective as, and with less complications than, percutaneous retrogasserian glycerol rhizotomy, when successfully administered. In fact, this approach

provides faster onset of pain relief with minimal complications (Stajčić 1989).

Pain relief provided by PGI could be attributed to the neurolytic effects of glycerol on the nerve bundle. It was postulated that the injected glycerol remained at the site of injection and caused compression of the nerve owing to its viscosity, thereby producing temporary anaesthesia or hypoesthesia which could account for the instant onset of relief for trigeminal neuralgic pain. Gradual penetration of glycerol into the centre of the nerve bundle disturbed osmolality equilibrium, resulting in axonolysis and demyelination of nerve fibres implicated in the trigger mechanism. This neurolytic effect is, however confined to the outer zone of the nerve bundle which could be responsible for the minimal sensory loss associated with PGI (Stajčić 1989; Al-Khateeb 1998). In an animal study, Al-Kateeb (1998) suggested that pain relief obtained with extraneural injection of glycerol is associated to the partial dehydration and compression of the involved nerve with minimal evidence of actual destruction.

In another study, PGIs were administered to 17 out of the 22 patients with uncontrolled TN that was previously treated by medication and cryotherapy. The outcome of PGI was poor. The mean pain-free period achieved was from 2-7.6 months, obviously lower than those injected with alcohol (1 month to 3 years) and the report by Stajčić (Fardy et al. 1994). This is in contrast with two more recent studies, with one reporting a mean pain-free period of 10.25 months (Sharma et al. 2012; Sohail et al. 2006). Sohail et al. (2006) reported that glycerol injection enabled patient to be pain free with minimal dose of medication. In addition, Fujimaki et al. (1990) has reported a median pain-free interval for 32 months with almost 28.4% of a total of 122 patients being successfully relieved of pain for 54 months. PGIs have been tried on paediatric patients with considerable success (Fujimaki et al. 1990). There was a wide range of sensory disturbance being reported in the literature after peripheral glycerol injection. Håkanson (1981) reported that 60% of his cases developed minor sensory disturbance on the face which resolved after several weeks with none of them having unpleasant paraesthesia. Lunsford and Bennett (1984) also reported 25.9% of patients having mild sensory disturbance while only 1.8% had major hyperaesthesia. Fujimaki et al. (1990) found that 63% developed mild alter sensory disturbance and 29% of painful dysaesthesia. In a study by Yue (2004) only two (11%) of the eighteen paediatric patients with trigeminal neuralgia were found to have sensory paraesthesia with only one being permanent. However, no obvious discomfort was perceived (Fujimaki et al. 1990). Sohail et al. (2006) reported that 16% of their patients complained of postoperative numbness at the site of injection. In half of these patients, resolution was seen within 3 months whereas the numbness persisted in rest of the patients for up to one year (Sohail et al. 2006). In contrast, other authors reported a minor sensory disturbance rate between 17% and 73% with 2%

to 34% being severe annoying sensory disturbance (Håkanson 1981; Fujimaki et al. 1990; Yue 2004; Dade & Marvin 1984). It is believed that repeated injection of glycerol transcutaneously in the recurrent TN might result in more sensory disturbance similar to those receiving alcohol block injection. Apart from glycerol or in its combination with local anaesthetic agents, the effect of a mixture of glycerol with 10% phenol has been reported once (Wilkinson 1999). Wilkinson in 1999 reported the outcome of 60 glycerol injections containing 10% phenol to eighteen patients. Eighty-seven percent of those receiving injections achieved remarkable or total pain relief initially. Of injections that provided initial relief, 37% remained pain-free after 1 year and 30% after 2 years. The median pain-free period was 9 months after each injection. The majority of patients with recurrent pain after months of pain relief requested another injection rather than subjecting themselves to a more invasive surgery. No severe complications or dysaesthesia were reported with this injection. Facial sensory loss was well-tolerated and generally recovered within 6 months (Wilkinson 1999).

In summary, although this procedure is associated with some notable complications, the recurrence rate from PGI is comparable to other more invasive surgical procedure adopted in the management of TN. PGI is easy and safe to be performed under local anaesthesia with apparently lower morbidity. It is effective for pain control, in comparison to peripheral alcohol injection. Like peripheral alcohol injection, PGI has also survived the onslaught of medical advancement and remains a mode of treatment in some less developed countries; for the elder and/or medically compromised patients, thoe drug-refractory trigeminal neuralgia patients or those unwilling to undergo neurosurgical procedures (Sohail et al. 2006). It could be considered as an alternative less invasive treatment for trigeminal neuralgia.

Streptomycin-local Anaesthetic Injections

Streptomycin is a broad-spectrum aminoglycoside antibiotic produced by the soil bacterial actinomycete Streptomyces griseus. It is the treatment of choice for active tuberculosis. Streptomycin also modulates excitatory neurotransmitters release at primary afferent nerve endings. It acts at phosphatidylinositol receptor in the neuronal membrane by competitively inhibit Ca^{2+} at this site to inhibit the transduction of pain (Lodhi et al. 1979). The injection of streptomycin for alleviating idiopathic trigeminal neuralgia (ITN) was first studied by Sokolovic et al. in 1986. A total 20 cases of either maxillary or mandibular branch TN were injected with 1-2 ml streptomycin sulphate (1 g) mixed with 2 ml of 2% plain lidocaine solution repeated in three to seven days interval for five times. All patients obtained pain relief immediately. Only four of the cases had recurrent pain at the same nerve distribution 18-30 months post injection, while the remaining 16 patients were pain free for a duration

up to 30 months (Sokolovic et al. 1986). Subsequently, Bittar and Graff-Radford (1993) found no statistically significant effect of streptomycin injection in term of pin-prick or light touch sensation in the involved nerves among twenty subjects. Generally, there was no reported permanent adverse effect from streptomycin injection (Sokolovic et al. 1986; Stajčić et al. 1990), except for facial swelling at injection site which resolved spontaneously within one-week with no residual complications (Bittar & Graff-Radford 1993). The mechanism of action for streptomycin nerve block remains unclear. However, the study of Sokoll and Diecke (1969) on intact frog sciatic nerve conduction had showed the nerve membrane stabilizing effect and non-specific local anaesthetic-like effect of streptomycin. Alkadhi and McIsaac (1978) studied the ganglionic blocking effect of streptomycin on rabbit and rat in 1978. The presynaptic effect of streptomycin reduces the release of acetylcholine. Streptomycin also has minor local anaesthetic effects and dose-related post-synaptic receptor blockade effects on nerve ending (low dose stimulation while high dose cause depression) as investigated by Sokoll and Gergis in 1981 (Sokoll & Gergis 1981).

Beside trigeminal neuralgia, streptomycin-lidocaine injections have also been used successfully for the management of cluster-tic syndrome, where cluster headache also present concurrently with TN (Kreiner 1996). Akhtar et al. (2016) examined the effect of the combination 0.5% bupivacaine and 1g streptomycin in various neuropathic condition and found that the combination provided excellent pain relief to trigeminal neuralgia as compared to post herpetic neuralgia and nerve entrapment pain. However, in comparing the effect of streptomycin/bupivacaine and glycerol injection, Khan et al. (2010) found no difference in the analgesic effect between both procedures; both were simple, quick and easy to perform as outpatient procedures.

Local Anaesthestic Injections

Local anaesthetic agents block sodium channels in neuronal membranes potently and inhibits spontaneous discharges in neurons of cases with neuropathic pain such as trigeminal neuralgia (Akhtar et al. 2016). They can act on various kinases included protein kinase C (PKC), guanosine triphosphate-binding protein (G protein) and other receptors which activate them (Akhtar et al. 2016). Local anesthestic agents have been injected into the Gasserian ganglion (Adler 1975) or administered as peripheral blocks for the treatment of TN throughout the past century.

The first local anesthestic agent synthesised was procaine (novocaine), an ester anaesthetic patented by Alfred Einhorn in 1905 (Dunsky 1997). As the first injectable man-made local anesthetic, procaine was administered to control TN. It had been given as peripheral blocks either alone (Livingston 1941; Verlocky & Weitzmann 1946; Sumanovac 1954), or in combination with alcohol (Woodbridge 1930; Kibets 1968) or platyphylline (Sheshelovskiĭ & Averchenko 1996). In addition,

Petrov (1951) reportedly gave intra-arterial injections instead of blocks. The injections of procaine were later superseded by lidocaine (lignocaine/xylocaine), an amide local anaesthetic synthesised by Nils Lofgren in 1943 (Holmdahl 1998). Because of its safety, it rapidly becomes the preferred local anaesthetic agent to provide temporary relief from TN. It was first marketed in 1948, following which, other derivatives such as bupivacaine and ropivacaine became available.

Not much has been reported on the use of lidocaine alone to manage TN, perhaps because of its similar outcome as procaine, minus the adverse effects. In 2008, Han et al. evaluated the effect of a highly concentrated lidocaine used as trigeminal nerve block in patients with TN. Almost one-third (31.4%) of their 35 patients experienced complete pain-free with markedly reduced general pain scores compared to pre-treatment scores (Han et al. 2008). Following the nerve block, the pain-free interval can range from 3 weeks up to 172 weeks. They suggested that the longer duration the pain free effect was partly related to the physical action of the local anaesthetic agent for inhibition in the adhesion of inflammatory cells and exudates from the nerve area. Instead of administering high concentration of lidocaine, application of a continuous mandibular nerve block with local anaesthetic agents using an indwelling catheter to control the TN pain was reported by Umino et al. (2002). A relook in 2015 on the effect of standard injections of 2% lidocaine has reported that in addition to routine pharmacotherapy, this combination provides clinical benefit in the management of TN (Di Stani et al. 2015). Di Stani et al. showed that patients given routine pharmacotherapy and 2-4 cc of 2% lidocaine injections have more reduction in the frequency of pain and exhibited a bigger improvement in pain scores, general health and depression scales during follow-up visits at 30 and 90 days, as compared to those receiving pharmacotherapy alone (Di Stani et al. 2015). In the same year, Stani and colleagues also reported superior pain relief effect when TN was treated pharmacologically and with local injection of 2% lidocaine (Di Stani et al. 2015). A more recent study reported that the neurolytic effect of 0.5% of lidocaine and 50% of ethanol was able to achieve complete cure for infraorbital nerve (Mahli & Coskun 2017). More recently, lidocaine in a higher concentration of 8% spray has been given through the nose for treating TN in the maxillary branch (Kanai et al. 2006).

Instead of injecting high concentration or continuous courses of local anaesthetic agents, the beneficial use of longer acting agents such as ropivacaine (Feldman & Covino 1988), mepivacaine (Goto et al. 1999) and bupivacaine have been reported. Concerns about the cardiotoxicity and central nervous system safety of bupivacaine led to the invention of ropivacaine which is a pure S-enantiomer. The overall clinical profile of ropivacaine is identical to bupivacaine in terms of onset, quality and greater duration of sensory block compared to motor block, considering

that it has high pKa and relatively less lipid soluble (Feldman & Covino 1988). This is an advantage for injections around the face. The evaluation of therapeutic effects of ropivacaine block in relation to gabapentin therapy showed improvement of pain scores (VAS) up to 4 weeks after the treatment (Lemos et al. 2008).

Dergin and his colleagues administered 0.5% plain bupivacaine locally via epidural catheter pump for 5 days and reported significant sustained reduction in the VAS score for 9 months. They advocated this alternative for patients who are contraindicated for anticonvulsants or neurosurgical intervention (Dergin et al. 2012). Goto et al. (1999) reported the synergistic effect of adding 4% tetracaine to 0.5% bupivacaine injections in 3 patients where the analgesic effects can last for more than 3 months compared to only several days by using the 0.5% bupivacaine or 1% mepivacaine. Two patients developed hyperesthesia within a week following the infraorbital nerve block, but the sensory disturbance disappear within two weeks (Goto et al. 1999). Goto et al.'s team followed up these case reports by comparing the use of high-concentration of 4% tetracaine dissolved in saline for the management of trigeminal neuralgia in comparison to 0.5% bupivacaine in 5 elderly patients (Radwan et al. 2001). They reported that the analgesic effect of tetracaine blocks continued for a median period of 2 months, irrespective of carrier used. The advantage of 4% tetracaine dissolved in 0.5% bupivacaine has been reconfirmed in another recent study from Japan (Takechi et al. 2017). They reported pain relief lasting up to at least 6 months, without any side effects of other neurolytic solutions.

Ketamine acts via peripheral mechanism to enhance the long-lasting analgesic effects of bupivacaine. (Tverskoy et al. 1996). Chang et al. (2003) thus treated TN by combining ketamine, morphine and bupivacaine in multiple peripheral nerve blocks. They claimed that pre-treatment pain intensity score of 8-9 was reduced greatly to 2-3 after the administration of these combined drugs. At three months follow up, pain was only controlled by conventional oral analgesics. No neurological disturbance was reported with this technique (Chang et al. 2003).

A different cocktail of local anaesthesia comprised of plain lidocaine, lidocaine with epinephrine, bupivacaine, fentanyl and clonidine was used by Naja et al. (2006) as repeated nerve blocks for trigeminal neuralgia. In their patients, initial pain scores of 8-10 disappeared for 1 month but gradually increased thereafter. Naja et al. (2006) then gave repeated injection every month for a year. They noticed following that; patients were pain free for the subsequent 9 months. Similar to the report by Chang et al. (2003), no neurological disturbances were associated with this treatment. Another substance which had been reported to be effective in treating TN was dexamethasone. Cok and colleagues injected 1% lidocaine with 1.5 mg of dexamethasone twice in a month to the infraorbital nerve of the patient guided by ultrasound. Although pain was not completely

eradicated, the patient reported a great reduction in the pain intensity for 21 months (Cok et al. 2017).

Injections of Botulinum Toxin

Botulinum toxin type A (BTX-A) is a neurotoxin produced by gram-positive obligate anaerobic bacteria called as *Clostridium botulinum*. From seven antigenic subtypes of BTX, only BTX-A is more potent and is widely used medically. It is believed to bind to a protein at presynaptic terminals of neuromuscular junction and inhibit the exocytosis of acetylcholine, thus inhibit the sympathetic transmission and muscle contraction. Nevertheless, the mechanism of its analgesic and antinociceptive effects remains unclear. Until recently, several studies have shown the inhibition effects of BTX-A on the release of several pain-related neurotransmitter such as glutamate, calcitonin gene-related peptide and substance-P. Therefore, it has been postulated that BTX-A is able to inhibit peripheral nociception directly and central nociception indirectly (Aoki & Guyer 2001; Guardiani et al. 2014). Success has been reported in the usage of BTX-A in pain syndrome such as chronic migraine, temporomandibular myofascial pain, occipital neuralgia and tic convulsive (Dodick et al. 2005). Following that, more clinical studies have been carried out to investigate the effectiveness and safety of BTX-A application in treatment of trigeminal neuralgia.

The approach for BTX-A injection as a treatment for trigeminal neuralgia was either subcutaneous or intradermal route at the trigger zones or dermatome (Wu et al. 2012; Zhang et al. 2014; Shehata et al. 2013; Zúñiga et al. 2008). Guardiani et al. (2014) has proposed that intradermal injection is superior as they believed the unmyelinated sensory nerve endings are located within the papillary dermis. Nevertheless, other literature also showed evidence of effectiveness in using subcutaneous injections because of the close proximity of unmyelinated sensory nerve ending to the papillary dermis (Shehata et al. 2013; Zúñiga et al. 2008). Another completely different method of 50 units bolus BTX-A injection given right above and below the zygomatic arch with mouth open slightly was used by Türk et al. (2005). Effective dosage of BTX-A varied among studies, from 20 units to 100 units (Wu et al. 2012; Zúñiga et al. 2008; Bohluli et al. 2011). Wu et al. (2012) applied 5 IU of BTX-A at 15 different trigger points which made up to total 75 IU; Zúñiga et al. (2008) used 20- 50 IU at painful trigger zone; and Xia et al. (2016) used a total of 100 IU at 15-20 trigger sites. The study of Zhang et al. (2014) comparing 25IU with 75IU demonstrated no significant difference in the improvement of pain intensity in short term. This showed that high dosage of BTX-A used might be unnecessary and further study needed to identify a more cost-effective lower dose to achieve the same effectiveness.

The proportion of patients responding to the BTX-A treatment, with at least 50% reduction in the frequency or intensity of pain ranged from 68% to 100% (Morra et al. 2016). This injection has a faster onset of

Table 1: Types of chemical agents used for peripheral nerve injection and their effect on trigeminal neuralgia.

Chemical agents	Dosage / Concentration	Effect
Alcohol	0.5 – 2.0 ml , 80-100% alcohol	Pain relief varies from 6 – 39 months depending on site of injection
Glycerol	99.9% anhydrous glycerol	Pain relief varies from 6 – 26 months
Streptomycin-local anesthetic	1-2 ml streptomycin sulphate (1g) mixed with 2 ml of 2% plain lidocaine	Pain relief varies from 18 – 30 months
	1g streptomycin with 0.5% bupivacaince	
Local anesthetic	Procaine 2-4 cc, 2% Lidocaine 0.5% Bupivacaine 1% Mepivacaine 4% Tetracaine	Pain relief varies from 3 weeks to 172 weeks
Botulinum toxin	20 - 100 units BTX-A	Pain relief up to 6 months

action and reaches a significantly therapeutic efficacy within 1-2 weeks and a maximum effect within 4-6weeks. The effectiveness for BTX-A was inconsistent among various studies with a relatively long duration of action which averaged three months. Bohluli et al. (2011) showed all of their 15 patients improved in frequency and intensity of pain up to six months duration with a complete eradication of the pain episodes. Further medication was not needed in seven of them. Türk et al. (2005) also reported the similar duration of benefit up to six months. Xia et al. (2016) even reported the analgesic effects of BTX-A lasting for two years in two TN patients. However, the duration of BTX-A therapeutic efficacy cannot be concluded as further studies with longer duration of follow-up which implement chronic pain score is needed.

BTX-A injections were generally well tolerated by most of the patients with no systemic reactions noted. However, some transitory adverse effect from BTX-A injections have been reported, including facial asymmetry, ptosis, swelling, haematoma, itchiness and pain on site of injection (Shehata et al. 2013; Morra et al. 2016). BTX-A offers a local, reversible and safe alternative treatment for trigeminal neuralgia with significantly faster and long-lasting pain relief without permanent systemic adverse effects. In cases of multidrug resistant or refractory TN, BTX-A can be a good alternative to spare them from invasive surgeries in the future.

CONCLUSION

As a conclusion, with evolution of time and technology, peripheral nerve treatments in trigeminal neuralgia will continue to provide promising outcome in alleviating the level of pain in trigeminal neuralgia. Despite the advancement in neurosurgery, peripheral alcohol injection and peripheral glycerol injection are still considered as a good alternative

especially in less developed areas or when patients general conditions do not permit neurosurgical interventions. Local anaesthetic injection also provides good relief of pain albeit non-total elimination of pain. The use of long acting local anaesthetic agents has greatly reduced the dosage and frequency of injection. Local anaesthetic agents had been combined with other drugs such as fentanyl, clonidine or streptomycin to produce a more sustained pain relief. Botulinium toxin is a relatively new addition to the list of agents used for peripheral nerve injection. It has been reported to produce a fast and long-lasting pain relief without permanent systemic adverse effects. A brief summary on the effect of each chemical agents is shown in Table 1.

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