RESEARCH ARTICLE

Intravenous lidocaine and magnesium on responses of A-δ and A-β nerve fibers at non-affected and affected areas in three cases of neuralgias

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Abstract:

Intravenous magnesium and lidocaine have been used for the management of intractable pain individually or in combination. A study reported on the positive effects when used in combination on neuralgia when antiepileptic drugs failed, but nobody has clarified how the combination works. The aim of the present case report is to see how a combination of intravenous magnesium and lidocaine influenced electrically-evoked responses of peripheral A-δ and A-β nerve fibers at non-affected and affected areas in three patients with neuralgia. For nociceptive stimulation, a method of intraepidermal electrical stimulation (IES) was used for the selective activation of cutaneous A-δ fibers, using a stainless steel concentric bipolar needle electrode. For tactile stimulation, similar cutaneous sites were stimulated for cutaneous A-β fibers using the same electrode. Three patients with intractable trigeminal neuralgia or intercostal neuralgia were treated using an intravenous infusion of a combination of 1.2g of magnesium and 100mg of lidocaine for one hour. Although all patients experienced sound pain relief after the combined intravenous infusion therapy, the combination had a different effect on electrically-evoked responses of peripheral A-δ and A-β nerve fibers at non-affected and affected areas in each patient.

Keywords: Intractable neuralgia; Intravenous magnesium; Intravenous lidocaine; peripheral A-δ and A-β nerve fibers

Introduction

The neuralgias are characterized by paroxysmal, brief and intense pains described as sharp, lancinating, stabbing, or lightning-like within the distribution of a particular nerve [1, 2]. Most patients benefit from medical therapy, such as carbamazepin, gabapentin and pregabalin [1-3], initially and for many years. Moreover, a combination of antiepileptic drugs can be an efficacious way to treat Trigeminal Neuralgia (TN) [3, 4]. Nonetheless, a number of patients suffer from severe and intractable pain, or the medications alleviate their pain but they experience intolerable side effects, leading to discontinuation. For such patients, a multimodality approach is necessary, such as a combination of non-antiepileptic drugs, Gamma Knife surgery and microvascular decompression surgery for TN and neurectomy, steroid injections, cryoablation and radiofrequency ablation for not only Intercostal Neuralgia (IN) but also TN [2, 3, 5, 6].

Intravenous magnesium and lidocaine have been used for the management of intractable pain individually or in combination [7-10]. Although we previously reported on the positive effects of the combination on TN when antiepileptic drugs failed [11], nobody has clarified how the combination works. We report here how a combination of intravenous magnesium and lidocaine influenced electrically-evoked responses of peripheral A-δ and A-β nerve fibers at non-affected and affected areas in three patients with neuralgia.

Case series

The present case series study was performed in three patients suffering from neuralgia who visited the pain center of Aichi Medical University Hospital. All patients were referred to the pain center from other hospitals. Since there are no tests to diagnose TN or IN, a correct diagnosis of TN or IN was based on the patient's medical history and description of their face or chest pain as well as a thorough neurologic examination [1-8]. Treatment protocols used in the present report were based on institutional policy and clinical guidelines approved by the IRB of Aichi Medical University. The treatment guidelines for patients with intractable neuropathic pain are as follows: Patients who are referred to the pain center will be treated while receiving the recommended systemic analgesics, although intravenous magnesium and lidocaine is not indicated for patients who are allergic to lidocaine. After receiving approval from the IRB of Aichi Medical University and the patients' oral consent, we administered the present case series study. All patients had an idiopathic form of neuralgia. The pathophysiological characteristics and therapeutic management

of the patients are described in Table 1. Patient 1 had been running out of medication for a month. Patients 2 and 3 had been taking an antiepileptic drug individually for a period of three to six months without satisfactory pain relief.

Table 1. Characteristics and treatment used in three patients with neuralgia.

Gender	Age (years)	Weight (kg)	Neuralgia	Pharmacological treatment (duration)
1 Male	44	54	Lt Trigeminal Ⅱ	No medication
2 Male	73	67	Rt Trigeminal Ⅱ	PGB 50mg/day (6 months)
3 Female	71	53	Rt Intercostal Ⅷ	PGB 75mg/day (3 months)

Abbreviations: Lt, Left; Rt, Right; PGB, pregabalin

Stimulation

For nociceptive stimulation, we used a modified method of intraepidermal electrical stimulation (IES) for the selective activation of cutaneous A-δ fibers [12]. In this study, we used a stainless steel concentric bipolar needle electrode (Nihon Kohden, Tokyo, Japan) for IES. The anode was an outer ring 1.3 mm in diameter and the cathode was an inner needle that protruded 0.1 mm from the outer ring. By pressing the electrode against the skin gently, the needle tip was inserted in the epidermis where nociceptors are located, while the outer ring was attached to the skin surface. The electrical stimulus was 2 triangular pulses of 1.2-ms duration (0.6-ms rise and fall) at an interstimulus interval of 20 ms. Three electrodes and double pulses were used to augment the response for temporal and spatial summation. For tactile stimulation, similar cutaneous sites were stimulated for A-β fibers distributed mainly in the cutaneous using the same electrode for A-δ fiber but only outer ring without needle part by monopolar stimulation (transcutaneous electrical stimulation, TS). The stimulus was 2 square pulses of 1.2-ms duration at an interstimulus interval of 20ms. Sensory thresholds of IES and TS were applied to the dorsum of the right hand and the affected areas (the cheek or the chest) and the sensory threshold was measured before and after the treatment. For IES, we started stimulation with an intensity of 0.01 mA and gradually increased the current in 0.01 mA increments until the subject felt a pricking sensation, and then gradually reduced the current in 0.01mA decrements to the point where the sensation disappeared. Usually, the pricking sensation disappeared with a decrease of 0.01 mA, but some subjects could feel a similar but weaker sensation at this intensity. Under the pain threshold, no sensations occurred in any subject. The upper limit of the intensity of IES was set at 1.0 mA. The threshold of tactile

sensations for TS was measured similarly.

Treatment and Effects

The treatment protocol was an intravenous infusion of a combination of 1.2g of magnesium and 100mg of lidocaine for one hour [11]. A numerical rating scale (NRS) for pain ranging from 0 to 10 (0= no pain, 10= worst pain imaginable) was evaluated and recorded before and after the treatment. Table 2 shows the individual changes of NRS and the pain threshold of IES and tactile threshold of TS. All patients experienced sound pain relief after the combined intravenous infusion therapy. In our preliminary study using twelve healthy subjects, the pain threshold of IES for the right hand, right foot, right chest and right cheek was 0.07-0.13, 0.09-0.14, 0.9-0.15 and 0.07-0.14mA, respectively and the tactile threshold of TS for the right hand, right foot, right chest and right cheek was 0.36-0.55, 0.40-0.65, 0.38-0.65 and 0.40-0.77mA, respectively. In Patient 1, thus, the thresholds of IES for the right hand and the right cheek were within the normal limits (0.06 and 0.13mA, respectively), but those of TS for the right hand and the right cheek were lower than the normal limits (0.18 and 0.12mA, respectively). In contrast, the threshold of IES for the affected area (the left cheek) was higher than the normal limit (0.25mA), but that of TS for the affected area was lower than the normal limit (0.23mA). After the treatment, the thresholds of IES for the right hand and the right cheek and the threshold of TS for the right cheek did not change (0.05, 0.12 and 0.13mA), but the threshold of TS for the right cheek increased (0.30mA). In contrast, the thresholds of IES and TS for the affected area (the left cheek) decreased (0.13 and 0.14mA). In Patient 2, the threshold of IES for the right hand was higher than the normal limit (0.70mA), but that of TS for the right hand was lower than the normal limit (0.15mA). In contrast, the threshold of IES for the affected area (the right cheek) was a little bit higher than the normal limit (0.18mA), but that of TS for the affected area was within the normal limit (0.48mA). After the treatment, the threshold of IES for the right hand decreased (0.20mA), but that of TS for the right hand increased (0.25mA). In contrast, the threshold of IES for the affected area slightly decreased (0.16mA), and that of TS for the affected area obviously decreased (0.15mA). In Patient 3, the threshold of IES for the right hand was higher than the normal limit (0.60mA), but that of TS for the right hand was lower than the normal limit (0.25mA). In contrast, the threshold of IES for the affected area (the right chest) was within the normal limit (0.10mA), but that of TS for the affected area was lower than the normal limit (0.48mA). After the treatment, the threshold of IES for the right hand

decreased to a normal limit (0.10mA), but that of TS for the right hand increased to a normal limit (0.45mA). In contrast, the threshold of IES for the affected area did not change (0.10mA), but that of TS for the affected area obviously increased to a normal limit (0.45mA).

Table 2. Pain scores and thresholds with each stimulus condition (TS and IES) before and after a combination of intravenous lidocaine and magnesium

	NRS	Threshold (mA)					
1 Male		Rt hand (IES)	Rt hand (TS)	Rt cheek (IES)	Rt cheek (TS)	Lt cheek (IES)	Lt cheek (TS)
Before IV	6	0.06	0.18	0.13	0.12	0.25	0.23
After IV	2	0.05	0.30	0.12	0.13	0.13	0.14
2 Male		Rt hand (IES)	Rt hand (TS)	Rt cheek (IES)	Rt cheek (TS)	-	-
Before IV	3	0.70	0.15	0.18	0.48	-	-
After IV	0	0.20	0.25	0.16	0.15	-	-
3 Female		Rt hand (IES)	Rt hand (TS)	Rt chest (IES)	Rt chest (TS)	-	-
Before IV	6	0.60	0.25	0.10	0.10	-	-
After IV	1	0.08	0.45	0.10	0.45	-	-

Abbreviations: NRS, numerical rating scale; Rt, Right; Lt, Left

Discussion

Neuralgias cause episodes of paroxysmal pain that are generally short-lasting (from less than one second up to two minutes) but intense in nature [1, 2]. Although carbamazepine is the first-line drug of choice in the treatment and a combination of antiepileptic drugs is provided in many cases, drug therapy sometimes results in severe side effects sufficient to warrant discontinuation and the pain becomes more intractable in some patients, which requires a multimodality approach [2, 3, 5, 6].

Lidocaine and magnesium are used safely in daily, clinical practice. Intravenous lidocaine is an amide local anesthetic with class I antiarrhythmic action [13]. Transmission of the peripheral nociceptive stimulus depends on the presence of voltage-gated sodium channels [14]. Lidocaine blocks impulses by inhibiting the sodium channels [15]. When used at sufficient concentration, local lidocaine causes a complete nerve block. When administered intravenously, lidocaine shows no apparent effects on the conduction of action potentials in normal Aβ, Aδ, or C afferent fibers [15]. In contrast,

intravenous lidocaine has a predominant effect on damaged neural tissues. Moreover, the administration of intravenous lidocaine blocks neuropathic pain through the action on sodium channels and blockade of the central hyper-excitability [7, 14, 15]. Activation of N-methyl D-aspartate (NMDA) receptors plays a key role in the induction and continuation of central and peripheral nerve sensitization [9]. Magnesium is an antagonist of the NMDA receptors and exerts the effects by physically occluding the receptor pore and allosterically modulating the NR2B subunit [16]. In fact, several studies showed significant benefits of magnesium on acute as well as chronic pain treatment [9, 10, 17].

Few reports showed the usefulness of a combined intravenous administration of lidocaine and magnesium in the management of intractable pain [10, 18]. A combination of intravenous lidocaine and magnesium provided sound pain relief for patients with intractable neuralgia in the present case series as shown in our previous case series [11]. Patient 1 was insensitive to the nociceptive stimulation at the affected area (the left cheek) but was sensitive to the tactile stimulation at not only the affected area but also the non-affected areas, which means that systemic neuromodulation might have occurred through the whole body because of the underlying neural circuits induced by the trigeminal neuralgia. The combination of intravenous lidocaine and magnesium made him less sensitive to the tactile stimulation at the right hand and more sensitive to not only the tactile but also nociceptive stimulation at the affected area (the left cheek), which means that the combination induced different neuromodulations at different parts. Patients 2 and 3 were insensitive to the nociceptive stimulation but were sensitive to the tactile stimulation at the non-affected area (the right hand). The thresholds of the nociceptive stimulation and the tactile stimulation at the affected area were within a normal limit in Patient 2, but Patient 3 was sensitive to the tactile stimulation at the affected area. These results mean that pregabalin made them insensitive to the nociceptive stimulation and sensitive to the tactile stimulation at the non-affected area, and pregabalin and neuralgias might have led to complicated neuromodulation at the affected area. Furthermore, the combination of intravenous lidocaine and magnesium nearly normalized the thresholds of the nociceptive stimulation and the tactile stimulation at the non-affected area in Patients 2 and 3, but the combination hardly influenced the threshold of the nociceptive stimulation and differently affected the thresholds of the tactile stimulation at the affected areas, which means that the combination could cause a very complicated systemic neuromodulation as shown in Patient 1.

A major limitation of the present report is that it is a case series. We need a randomized controlled trial. Furthermore, another major limitation is we did not investigate the effects of neuralgia per se and pregabalin nor the individual effect of magnesium and lidocaine on systemic neuromodulation. However, the incidence of TN is about 4 per 100,000 persons per year [3], the incidence of intractable TN would be much lower than this figure and we treat no more than 4 patients with intractable TN or IN a year in our clinical practice, so it is very impractical for us to administer a randomized, placebo-controlled trial.

In conclusion, we treated three patients with intractable TN or IN by using an intravenous infusion of a combination of 1.2g of magnesium and 100mg of lidocaine for one hour. Although all patients experienced sound pain relief after the combined intravenous infusion therapy, the combination had a different effect on electrically-evoked responses of peripheral A-δ and A-β nerve fibers at non-affected and affected areas in each patient.

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Competing interests: All the authors declare that they have no competing interests.

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Authors' contribution

Young-Chang Arai conceived of the study. Makoto Nishihara, Tatunori Ikemoto, Hironori Saisu and Keiko Owari participated in its study and conducted the acquisition of data. Young-Chang Arai, Makoto Nishihara and Tatsunori Ikemoto helped to draft the manuscripts. All authors read and approved the final manuscript.

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