Preliminary Report

Long-term epidural ketamine, morphine and bupivacaine attenuate reflex sympathetic dystrophy neuralgia

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Purpose: There is considerable evidence that NMDA receptor antagonists can abolish nociceptor hypersensitivity in animals. In the present case report, two patients with reflex sympathetic dystrophy were treated with ketamine, a NMDA antagonist, morphine and bupivacaine.

Clinical features: Two patients were referred suffering from severe pain, allodynia, hyperaesthesia, swelling and disability over their right lower legs, diagnosed as reflex sympathetic dystrophy. They had received conventional treatments with non-steroid anti-inflammatory drugs (NSAIDs), steroids, anticonvulsant, antidepressant, epidural lidocaine sympathectomy and rehabilitation which failed to provide satisfactory pain relief. We administered subanalgesic doses of ketamine (7.5 mg), morphine (0.75 mg) and 6 ml bupivacaine 0.1% via a lumbar epidural catheter three times per day. After several courses of treatment over three and six months, satisfactory pain relief was achieved in each patient. Both are now able to walk with slight weight bearing with the assistance of crutch. The treatment is continuing with further improvement of symptoms and signs.

Conclusion: Epidural coadministration of low doses of morphine, ketamine and bupivacaine provided effective pain relief in two patients. This suggests synergy from this combination that provides an alternative treatment for reflex sympathetic dystrophy.

Objectif : Il existe de nombreuses preuves que les antagonistes des récepteurs N-méthyl-D-aspartate (NMDA) peuvent abolir l'hypersensibilité nociceptive chez les animaux. Dans cette présentation de cas, deux patients présentant une dystrophie sympathique réflexe ont été traités avec de la kétamine, un antagoniste NMDA, de la morphine et de la bupivacaine.

Éléments cliniques : Deux patients ont été adressés pour dystrophie sympathique réflexe de leur jambe droite distale. Ils présentaient de la douleur sévère, de l'allodynie, de l'hyperesthésie, du gonflement et de l'invalidité du membre. Ils avaient reçu des traitements conventionnels, soit anti-inflammatoires non-stéroïdiens (AINS), anti-convulsivant, antidépresseur, sympathectomie chimique par lidocaïne péridurale et réhabilitation, le tout sans soulagement adéquat de la douleur. Nous avons administré 3 fois par jour des doses subanalgésiques de kétamine (7.5 mg), de morphine (0.75 mg) avec 6 ml de bupivacaine 0,1 % par un cathéter péridural lombaire. Après plusieurs périodes de traitement réparties sur trois et six mois, un soulagement satisfaisant de la douleur a été obtenu chez chaque patient. Les deux sont maintenant capables de marcher avec mise en charge partielle et assistance d'une béquille. Le traitement se poursuit avec amélioration continue des signes et symptômes.

Conclusion : L'administration concomitante de doses faibles de kétamine, de morphine et de bupivacaine a entraîné un soulagement efficace de la douleur chez deux patients. Ceci suggère une combinaison synergique qui permet une autre option thérapeutique pour la dystrophie sympathique réflexe.

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THE NMDA receptor antagonist ketamine, in combination with morphine and local anaesthetic, has been used previously via the epidural route for relief of postoperative and neuropathic pain management.¹⁻³ In this report, we describe two patients with severe neuralgia of reflex sympathetic dystrophy (RSD) in whom conventional treatment had failed to relieve the pain. Epidural administration of long-term epidural ketamine (7.5 mg), morphine (0.75 mg) and bupivacaine (0.1%) successfully relieved the neuropathic pain and improved their functional activity.

Case #1

A 23-year old man had suffered from RSD with pain, swelling and cold sensation over the right lower leg for five months. Severe allodynia and hyperaesthesia were also noted. A pain score of 9 on a scale of 10 was reported using a visual analog scale (0 to 10). Conventional pain management with indomethacin, prednisolone, cabamazepine, imipramine and local anaesthetic induced sympathectomy, had only a poor response. The patient was unable to tolerate rehabilitation due to severe allodynia and hyperalgesia. With the patient's written consent, an 18-gauge epidural catheter was introduced at the L₃₋₄ level and advanced caudally for 5 cm. Ketamine (7.5 mg) and morphine (0.75 mg) in 6 ml bupivacaine (0.1%) were administered epidurally. The pain intensity gradually reduced to 6/10. This analgesia lasted for five hours and rehabilitation activity could be performed. The treatment was continued every 12 hr for 9 days and the epidural catheter was removed due to erythematous change around the puncture site. One month later, a second course of treatment was given for 11 days. The treatment interval was reduced to eight hours because pain relief could not be maintained with the 12-hourly treatment. After four courses of treatment within three months, the patient was transferred to a chronic hospital with 50% improvement of the original symptoms. Unfortunately, allodynia, and hyperalgesia worsened within a month. The patient was transferred to our hospital for lumbar sympathectomy which he refused. Another five courses of 10 to 14-day treatment were given. All the symptoms subsided except for a slight limitation of active plantar flexion. Currently, he can walk with slight weight bearing of his right leg without any medication. Treatment is summarised in Table I.

Case #2

A 24-yr-old man was referred with the diagnosis of RSD over the right lower leg for three months. He had injured his right rectus femoralis during the military training and the muscle damage was repaired two

months after injury. Unfortunately, two weeks after surgery, pain, swelling and weakness developed over his right lower leg and was followed by a burning sensation to cold. With failure of conventional treatment, he was referred for pain management. With patient's written consent, the same treatment regimen, as described in case #1, was given. The pain score was 9/10 before treatment and after four courses of treatment over three months, 50% improvement was achieved in pain and allodynia. Swelling and cold hypersensitivity subsided gradually. The dark right ankle was noted only when in a dependent position. After another three courses of treatment, he was transferred to a chronic hospital and discontinued the treatment. Currently, the patient is satisfied with the treatment and, with progressive improving of symptoms, can tolerate the rehabilitation programme well. The treatment is summarised in Table II.

Discussion

This preliminary report demonstrates that epidural administration of subanalgesic doses of ketamine and morphine with a low concentration of bupivacaine reduced neuralgia of RSD and allowed a rehabilitation programme to be commenced. Nerve injury may cause a pathological interaction between sympathetic and

TABLE I The treatment courses of Case #1.

Course	before	1	2	3	4*	5	6	7	8	9	10	11
Pain†	9	6	6	5	5	8	6	4	2	1	1	1
Allodynia‡	+++	+++	++	++	+	+++	++	+	-	-	-	-
Colour§	p	p	p	d	d	d	d	pi	pi	pi	pi	pi
Temperature¶	c	c	c	w	w	c	c	w	w	w	w	w
Swollen‡	++	++	+	+	-	++	+	+	-	-	-	-

* Patient was transferred to another hospital and discontinued the epidural treatment.

† Visual analog pain score from 10 (worst pain) to 0 (no pain).

‡ "+++" = severe, "++" = moderate, "+" = mild, "-" = none.

§ Skin colour: p = purple, d = dark, pi = pink.

¶ Skin temperature: c = cold, w = warm.

TABLE II The treatment course in Case #2.

Course	before	1	2	3	4	5	6	7
Pain*	9	8	7	5	4	4	3	2
Allodynia†	+++	+++	++	+	+	-	-	-
Colour‡	p	p	d	d	d	d	pi	pi
Temperature§	c	c	w	w	w	w	w	w
Swollen¶	+++	++	++	+	+	-	-	-

* Visual analog pain score from 10 (worst pain) to 0 (no pain).

† "+++" = severe, "++" = moderate, "+" = mild, "-" = none.

‡ Skin colour: p = purple, d = dark, pi = pink.

§ Skin temperature: c = cold, w = warm.

somatosensory nervous systems that induces a neuro-pathic pain syndrome. Reflex sympathetic dystrophy comprises a complex disorder that usually develops after trauma and in which pain is the cardinal feature. According to Roberts, RSD may be a physiological response to an external insult.⁴ He suggested that a reflex mechanism may sensitise the wide dynamic range (WDR) neurons in the spinal cord and result in excessive sympathetic outflow and neuropathic pain. Consequent vasomotor and dystrophic changes in the affected limb serve to maintain the input to this reflex and spread the condition by stimulation of mechanoreceptor afferent neurons rather than the nociceptive neurons.

Many treatment modalities exist but with inadequate pain relief that limits active rehabilitation. Oral medication with NSAIDs, α -adrenergic antagonists, anticonvulsants, antidepressants, and corticosteroids have been used for pain management with limited effect. Intravenous regional blocks with guanethidine have been widely used in the management of RSD, but with reported successful results varying from 6 to 100%.⁵ Koniz reviewed seven studies and found approximately 46% of patients had satisfactory pain relief by sympathetic ganglion block.⁶ Epidural clonidine was an effective treatment of RSD although its use was limited by sedation and hypotension.⁷ Also, the response to opioids is poor in patients with RSD.⁸

The NMDA receptor has been demonstrated to be involved in nociception modulation in the spinal cord. Nagasaka *et al.* revealed that ketamine reduced the excitatory and inhibitory responses of WDR neurons in transected spinal cord.⁹ Kishimoto *et al.* first reported that intravenous ketamine infusion combined with stellate ganglion block and continuous epidural block completely relieved the symptoms of RSD.¹⁰ Recently, we successfully treated neuropathic pain syndromes with the same epidural pain control regimen as used in this report.³⁻⁴ In this preliminary report, not only pain but also swelling and skin temperature change improved after the treatment. No ketamine- or morphine-associated side effects were noted during treatment. Furthermore, the neurotoxicity of ketamine, and tolerance and dependence to morphine were not observed after long-term epidural administration. Repeated epidural catheter insertion may cause scar formation and adhesion of the epidural space that may limit the drugs distribution, but this did not occur in these cases. Implantation of the catheter may eliminate the problem.

Early rehabilitation is essential for the treatment of RSD and, therefore, multi-disciplinary pain management should be carried out. In this report, we demonstrated that epidural coadministration of subanalgesic

doses of ketamine and morphine with a low concentration of bupivacaine effectively attenuated the neuralgia and allodynia of RSD as well as other hyperactive sympathetic symptoms that enhanced the rehabilitation program. The result suggests pharmacological synergy between morphine, ketamine and bupivacaine. However, this will require a rigorous controlled study to confirm the effectiveness of this treatment and its possible mechanisms.

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