Continuous Brachial Plexus Analgesia and NMDA-receptor Blockade in Early Phantom Limb Pain: A Report of Two Cases

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ABSTRACT

Objective. To provide a mechanism-based acute pain management strategy for early phantom limb pain following traumatic amputations and to collect first evidence of its acute and potentially preventative effects on the formation and maintenance of phantom limb pain. The combination of continuous brachial plexus analgesia and prolonged block of N-methyl-D-aspartate (NMDA) receptors over 4 weeks aimed to attenuate peripheral and central sensitization, currently thought to be substantially involved in establishing and maintaining phantom limb pain.

Case Report. Two patients, after traumatic upper limb amputations and early phantom limb pain, were treated on the second and fifth day following amputation by continuous brachial plexus analgesia with ropivacaine 0.375% (30 ml for the initial block, continuous infusion rate = 5 ml/h) for 5 (Patient 1) and 9 days (Patient 2). Both patients received oral memantine (a noncompetitive NMDA-receptor antagonist) in increasing doses from 10 to 30 mg/d over a 4-week period. Ropivacaine only produced minor motor block, with almost unimpaired motor function. Memantine was well tolerated and no relevant side effects were observed. In both patients the treatment prevented the establishment of phantom limb pain, which did not reappear during follow-up of 1 year.

Conclusions. The combination of long-term regional analgesia with prolonged block of NMDA receptors might be effective for treatment and prevention of phantom limb pain following traumatic amputations. The absence of clinically relevant side effects, together with maintained motor function suggests this treatment to be a promising preventive strategy for phantom limb pain following traumatic amputations.

Key Words. Central Sensitization; Memantine; NMDA antagonist; Phantom Pain; Prevention

Introduction

Following upper limb amputations, the reported incidence of phantom limb pain varies from 67% to 87% [1]. Preamputation pain and, above all, the occurrence of phantom limb pain early after amputation are valid predictors for the persistence of chronic phantom pain [2]. To date, effective treatment of established chronic phantom limb pain remains a challenge [2-4]. Growing insights into the underlying pathophysiology demonstrate that functional and structural plastic changes in nociceptors, spinal cord neurons, and subcortical and cortical structures are involved in the formation and maintenance of chronic neuropathic pain, of which phantom limb pain is a subset [5-8]. Following amputation, prolonged nociceptive barrage triggers a pathophysiological cascade leading to sensitization in peripheral and central nociceptive pathways, and subsequently, to the formation of chronic pain [4,6-8]. Sensitization processes at the spinal level are primarily mediated by N-methyl-D-aspartate (NMDA) receptors, which seem to play an essential role in the development of chronic pain states and the shaping of pain memory [4,5,9].

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Accumulating experimental and clinical evidence suggest that NMDA-receptor mediated central sensitization may be successfully blunted by NMDA-antagonists in early disease stages [5,9,10]. We report on two patients with early phantom limb pain after traumatic upper limb amputations who received continuous brachial plexus analgesia for 5 and 9 days, respectively, combined with oral memantine (a noncompetitive, low-affinity NMDA-receptor antagonist) over 4 weeks.

Methods

After approval of the treatment protocol by the Ethical Review Board and informed written consent, patients received the following treatment.

Continuous Brachial Plexus Analgesia

With standard anesthesia monitoring (noninvasive blood pressure, electrocardiogram, pulse oximetry), brachial plexus catheters (Contiplex®, B. Braun AG, Melsungen, Germany) were placed under neurostimulator guidance (Stimuplex®, B. Braun AG, Melsungen, Germany) via the axillary (Patient 1) and vertical infraclavicular approaches (Patient 2). Following an initial bolus of 30 ml of ropivacaine 0.375% (Naropin®, AstraZeneca, Wedel, Germany), continuous analgesia was maintained with an infusion of 5 ml/h ropivacaine 0.375% for 5 days in Patient 1 and 9 days in Patient 2. Recurring pain due to a regression of the blockade was treated with bolus injections of 20-30 ml of ropivacaine 0.375%. Sufficiency of the block was tested daily by pinprick in the innervation areas of radial, musculocutaneous, median, ulnar, medial cutaneous, medial antebra-chial cutaneous, and axillary nerves, as far as permitted by the extent of amputation. Motor skills were monitored with a 6-point scale: 0 = paralysis; 1 = visible contractions without motor effect; 2 = movement when eliminating gravity; 3 = movement overcoming gravity; 4 = movement against resistance; 5 = normal motor skills.

Memantine

Memantine (Akatinol®, Merz and Co., Frankfurt, Germany) is a selective noncompetitive NMDA-receptor antagonist that has been reported to be clinically well tolerated [11]. Memantine, chosen because of its availability in tablet form, was administered orally in increasing dosage over 4 weeks (first week =10 mg/d, second week = 20 mg/d, third/fourth week = 30 mg/d). Adverse effects (nausea, fatigue, dizziness, agitation, and headache) were recorded on self-rating scales using 100-mm Visual Analogue Scales (VAS) (endpoints were “not at all” and “extremely”).

Pain Assessment

One hundred-mm VAS were used to record: Wound pain (wp); Stump pain (sp); Phantom pain (pp) (endpoints were “not at all” and “unbearable”); Stump sensations (ss); and Phantom sensation (ps) (endpoints were “not at all” and “most intense”) during the treatment period and in follow-up examinations after 4 weeks, 6 months, and 12 months.

Case 1

A 52-year-old male metalworker suffered a subtotal amputation of digit II (D II) and severe soft tissue injury of the left hand. Initially, soft tissue repair and amputation at the base of D II were performed with brachial plexus anesthesia. On the fifth day postinjury, the patient presented rapidly evolving phantom limb (VAS 60) and wound pain (VAS 58), despite intermittent ropivacaine boluses. The catheter was found to be dislodged, was removed and replaced, and oral memantine was started. Sixty minutes following the initial ropivacaine bolus, he was pain free. On Days 2, 3, and 4, less intense intermittent phantom pain recurred (VAS 40, 30, and 12 respectively), which was successfully blunted by top-up boluses of 20 ml of ropivacaine 0.375%. Continuous ropivacaine infusion produced a weak motor blockade (4 points). From Day 4, the patient remained pain free and ropivacaine was discontinued on day 5. Memantine was well tolerated and no side effects were observed. Phantom limb pain did not recur in the follow-up examinations after 4 weeks, 6 months, and 12 months.

Case 2

A 24-year-old carpenter lost left digits II and III totally, digit I in the distal, and digits IV and V in the proximal interphalangeal joint levels, together with major soft tissue injuries of palmar and dorsal mid-hand. The extended defect was covered by a vascularized flap mobilized from the groin. On the first day postinjury, he presented because of phantom limb (VAS 60) and wound pain (VAS 35) in the groin. A brachial plexus catheter was placed via the vertical infraclavicular approach and memantine was started. After the initial bolus of 30 ml of ropivacaine 0.375%, phantom pain (VAS 20) decreased. Persistent wound pain in the groin (VAS 10) was effectively treated with metamizole (4 × 1 g/d). On the second treatment day, phantom pain further
decreased to VAS 10, and on the third day to VAS 0. Phantom pain did not recur. Wound pain remained tolerable (VAS 8-15) under metamizole. The plexus catheter was removed on Day 10. Ropivacaine infusion produced a weak motor block (4 points). Memantine was well tolerated and no side effects were observed. Phantom limb pain did not recur and the patient remained pain free on all follow-up examinations (1, 6, and 12 months).

Discussion

Treatment of chronic phantom limb pain remains a clinical problem. Once chronic phantom pain is established, effective pain relief may be difficult to achieve [2,4,5,7]. Strategies to prevent the development of chronic phantom pain are, therefore, greatly needed. The concept of preemptive analgesia aims at preventing acute postoperative or chronic pain states by applying analgesic measures before the actual tissue damage occurs. Studies that have clinically tested this hypothesis yield inconsistent results [12].

Although clearly positive results of preemptive analgesia have been demonstrated in experimental animal models, clinical evidence so far remains disappointing [2,12]. Only a rather small body of literature concerning the prevention of phantom limb pain exists [2,13,14]. Inconsistent results and considerable methodological differences in sample size and experimental design do not allow a conclusive interpretation.

However, most published reports have focused on lower limb amputations, which are mainly performed as a consequence of occlusive arterial disease. Before amputations, the majority of these patients suffers from long-term preamputation pain [2,13,14]. Consequently, substantial sensitization of nociception may already have occurred long before the amputation. In this setting, preemptive or preventive analgesia, therefore, may not be effective in reversing an already established pain memory [4,12].

Recently, Nikolajsen et al. studied the effect of memantine at a dosage of 20 mg/d on spontaneous or evoked pain in patients with chronic neuropathic pain (duration of pain between 1 and 28 years) following amputation or surgery [15]. They did not find a reduction in spontaneous or evoked pain following memantine in chronic phantom limb pain. However, the question remains whether a prolonged block of NMDA-receptors in combination with a sufficient long-term acute pain management strategy might be effective in attenuating the formation of phantom limb pain in early disease stages. For this treatment approach, traumatic amputations might be a good model, since central sensitization due to prolonged preamputation pain can be excluded.

In animal studies, blockade of NMDA receptors at the spinal level prevented the development of neuropathic pain. The NMDA receptor, which is primarily responsible for induction and maintenance of central sensitization and establishment of a pain memory, might be a key structure at which to direct pharmacologic strategies to prevent and treat phantom limb pain [4,12]. Experimental evidence suggests that NMDA-receptor antagonists may be effective if used early in the course of phantom pain. An optimal strategy might be the preventive use of NMDA-receptor antagonists immediately after traumatic amputation. The two cases reported here suggest that NMDA-receptor antagonists may be helpful in treating acute, and preventing the establishment of chronic, phantom limb pain. This hypothesis is supported by the observation that phantom pain occurring soon after amputation is a valid predictor for the development of chronic phantom pain [2]. However, with respect to the small sample size, it has to be emphasized that the positive effect observed here cannot explicitly be attributed to the NMDA-receptor antagonist, memantine, or distinctively separated from the effect of an early-onset and continuously maintained regional anesthetic block. It also seems of importance to note that, with the exception of metamizole to control surgical pain in the groin in patient two, no concomitant analgetics, such as opioids or nonsteroidal anti-inflammatory drugs, with a potential impact on the reported effect were used.

Another limitation might be seen in the relatively small extent of amputation in the cases reported here. To date, the relation of phantom pain incidence and intensity to the size of amputation remains controversial. Growing evidence suggests that there is no correlation between phantom pain incidence and the level of amputation [16]. However, it remains unclear if severity of phantom pain might be related to amputation size. Kooijman and colleagues, in an epidemiological study, showed a tendency toward more intense phantom pain for amputations above the elbow compared with amputations below the elbow [1]. In contrast, disabling severe phantom pain with substantial reorganization of the primary somatosensory cortex (SI), has been observed after amputations of a single digit [17].

The clinical use of NMDA-receptor antagonists is limited because of frequent and sometimes seri-
ous side effects, such as dizziness, excitation, sedation, nausea, and psychiatric effects, such as illusions, visual disturbances, hallucinations, and altered body sensations [9-11]. However, memantine has been reported to be clinically well tolerated. Adverse effects were observed with rapid increases in dosage or use in combination with dopaminergic drugs [11]. Both cases reported here tolerated memantine well with no clinically relevant side effects. The superior tolerability of low-affinity channel blocking (uncompetitive) NMDA-receptor antagonists, such as memantine, is explained by their pharmacological and pharmacokinetic properties. Current theories explain this clinically favorable profile by a lower affinity to phencyclidine (PCP)-binding sites of the NMDA receptor, fast blocking and unblocking kinetics, reduced closed-channel block, and allosteric block at voltage-independent binding sites [11,18].

For the treatment of postamputation pain, we noted that ropivacaine 0.2% did not produce reliable analgesia. Ropivacaine 0.375% was found to produce sufficient analgesia, together with only weak motor block. It has been suggested that disturbance of motor function might also have an effect on the development of phantom pain [19]. Sustained somatosensory input from the stump, together with muscular training might be superior to a complete sensory and motor block, which potentially aggravates deafferentation pain due to deprivation from functional use [16].

Conclusions

In conclusion, this report adds evidence for the effectiveness of NMDA-receptor antagonists combined with regional anesthesia in attenuating the establishment and maintenance of chronic phantom limb pain, when performed early and in patients free of longstanding preamputational pain [4-7,10,12]. However, the observed beneficial effect of NMDA receptor blockade in combination with regional analgesia in the treatment of phantom limb pain needs to be confirmed by larger controlled clinical trials.

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