Prospective Evaluation

A Negative Correlation Between Hyperalgesia and Analgesia in Patients with Chronic Radicular Pain: Is Hydromorphone Therapy a Double-Edged Sword?

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Background: Opioids are the cornerstone therapy for the treatment of moderate to severe pain. Yet, unconfirmed evidence suggests that chronic exposure to opioids may cause hypersensitivity to pain, a phenomenon known as opioid-induced hyperalgesia (OIH).

Objectives: The current preliminary prospective study was aimed to explore the relationship between experimental OIH and clinical opioid induced analgesia (OIA) in a model of experimental OIH in patients with chronic radicular pain using intermediate-term opioid therapy.

Study Design: Prospective evaluation

Setting: Interdisciplinary Pain Clinic at a referral Health Care Campus

Methods: Thirty patients with chronic neuropathic (radicular) pain were assessed prior to and following 4 weeks of an individually titrated dose of oral hydromorphone treatment (4-20 mg/d). The assessments included an evaluation of experimental OIH by testing for heat pain intensity and cold pain tolerance and an assessment of OIA by completing pain and disability questionnaires.

Results: Hydromorphone was found to induce hyperalgesia, as measured by an elevation of phasic heat pain intensity ($P < 0.05$). At the same time, hydromorphone caused significant clinical analgesic effects. There was a notable reduction in average daily pain scores (primary analgesic outcome) of 26 Visual Analog Scale (0-100) points. A significant negative correlation was found between OIH and all OIA measures ($r = -0.389$, $P < 0.05$ for the primary analgesic outcome). Hydromorphone dosage was positively correlated with OIH ($P < 0.01$, $r = 0.467$) and negatively correlated with OIA parameters ($r = -0.592$, $P < 0.01$ for the primary analgesia outcome).

Limitations: The nonrandomized, open-label, prospective evaluation.

Conclusion: A 4-week regimen of open-label hydromorphone therapy results in a dose-dependent OIH, which negatively correlates with its analgesic effect. Future randomized, controlled, and blinded studies are needed to verify these preliminary results.

Key words: Opioid-induced hyperalgesia (OIH), analgesia, hydromorphone, neuropathic pain, disc herniation, radiculopathy.

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Although the efficacy of opioids for reducing neuropathic pain is high (1), there is still a huge variability in the magnitude of each patient's response to opioids. Several explanations for this variability have been suggested, including pharmacokinetic variations (2), gender (3), and genetic characteristics (4). Yet, this variability is still not fully explained.

Apart from potential side effects, tolerance, and addiction, opioid use can be associated with another

phenomenon, referred to as opioid-induced hyperalgesia (OIH). OIH is defined as a state of nociceptive sensitization caused by exposure to opioids and characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain actually becomes more sensitive to pain (5). Animal studies suggest that the administration of opioids may paradoxically increase nociception and potentially aggravate preexisting pain-like behavior (6-8). However, evidence regarding the existence and importance of OIH in humans is not as clear-cut, especially in clinical settings (9). On the one hand, OIH in the postoperative period has been reported following the administration of short-acting opioids during surgery (10-13). Additional evidence comes from opioid addicts on methadone maintenance therapy, in whom decreased tolerance to cold pain (as measured by time to hand withdrawal from ice-cold water) has been reported (14-16). On the other hand, mixed results are found regarding hyperalgesia in patients with chronic pain who receive intermediate-term opioid treatment (17-21). In some studies, no evidence of OIH could be demonstrated (17,19) whereas, a few "snapshot" studies did demonstrate altered pain perception (17,20).

Yet, prospective studies demonstrating the development of OIH in patients with chronic pain are generally lacking. One exception is a small prospective study (18) in which OIH during remifentanil infusions was notable in 6 patients with chronic back pain after one month of oral morphine treatment when compared to baseline values. Yet, the same group of researchers failed to demonstrate OIH in a larger prospective study (22). Additional indirect evidence for OIH comes from another prospective study of patients with chronic pain receiving intermediate-term opioid treatment who attended a pain rehabilitation program, which included the cessation of opioid use. Heat pain thresholds were increased at the end of the program compared to their levels prior to enrollment (23).

Nonetheless, the existing literature regarding this specific population is meager and prospective studies aimed at understanding the extent and significance of OIH are lacking (9). Thus, the current open-labeled, preliminary prospective study was aimed at exploring the relationship between experimental OIH and clinical opioid induced analgesia (OIA) in a model of experimental OIH in patients with chronic radicular pain using intermediate-term opioid therapy. Based on the existing literature, our working hypothesis was that experimental OIH in response to hydromorphone therapy would be exhibited in some patients, and that its magnitude would negatively correlate with the extent of the demonstrated clinical analgesia.

Methods

Subjects

The study population consisted of 30 patients suffering from moderate to severe chronic lumbar radicular (neuropathic) pain, who were recruited either from the Institute of Pain Medicine at Rambam Health Care Campus or in response to an advertisement in the local newspaper. The diagnosis of radicular pain was made by pain specialists and met the new suggested International Association for the Study of Pain criteria for the diagnosis of neuropathic pain, as follows: anamneses, neurological examination, and objective laboratory tests, including computed tomography, magnetic resonance imaging, and electromyography (24). Inclusion criteria were: pain projecting from the lower back to one lower limb, at a distribution of one specific dermatome, for a duration of at least 3 months; pain attributed to lumbar disc herniation, meaning that magnetic resonance imaging and/or computed tomography scan findings were consistent with clinical symptoms in terms of side and level of the herniated disc; positive/negative sensory findings on neurological examination; positive straight leg raising/femoral stretch test in patients with lower/upper lumbar disc herniation (below/above L4), respectively; pain intensity above 4/10 on a visual analog scale (VAS) at rest; willingness to discontinue all previous analgesic medications (with the exception of acetaminophen) for a washout period of 7 days and subsequently to consume opioids for at least one month; candidacy for intermediate-term opioid therapy for nonmalignant pain, as determined by the treating physician; and ability to understand the purpose and instructions of the study and to sign an informed consent. Exclusion criteria were: presence of peripheral neuropathy of any etiology; presence of any other type of pain in any body region; use of antidepressants and/or anticonvulsants; pregnancy; allergy, history of substance abuse, or any other contraindication for the use of opioids; or a diagnosis of Raynaud Syndrome.

In addition, a group of 10 healthy patients were recruited as controls.

Instruments

1. The Cold Pressor Test (CPT) apparatus (Heto Cooling Bath CBN 8-30 Lab equipment, Allerod, Denmark) is a temperature-controlled water bath with a maximum temperature variance of ± 0.5°C, which is continuously stirred by a pump.

2. The Thermal Sensory Analyzer (TSA, Medoc, Israel, 2001) is a Peltier surface stimulator of 30X30 mm, which is used to administer painful thermal stimuli. The device was attached to the ventral surface of the dominant forearm with a hook-and-loop strap and was maintained at a baseline temperature of 32°C. A rise rate of 1C°/s to the destination temperature and a fall rate of 1C°/s to the baseline temperature were used.

Pain Measures

Evaluation of evoked experimental pain

Experimental method to induce phasic heat pain

As a previous study failed to show hyperalgesia to heat pain threshold in response to a one-month regimen of oral morphine treatment in patients with low back pain (18), we chose to test an alternative heat pain parameter. Thus, a heat stimulus was administered to the dominant volar aspect of the forearm. The temperature was increased from baseline until it reached the destination temperature of 46.5°C, which was then maintained constantly for a duration of 120 seconds. Pain intensity was recorded on a computerized Visual Analog Scale (0-100). Previous unpublished experiments in our laboratory showed that at this setting, after reaching the destination temperature, pain intensity initially peaks (termed "phasic pain response"), then typically drops to some degree, and subsequently either gradually increases or declines (i.e., tonic pain). In the present experiment, we were interested in evaluating the phasic heat pain response only, and we therefore used that initial peak pain reading in all analyses.

Experimental method to induce cold pain

The CPT was used to induce cold pain stimuli by immersing the patient's hand in a 5°C water bath. Patients were informed that an initial cold sensation would soon become painful and were instructed to keep their hand immersed in the cold water until they could not tolerate the pain any longer. Typically, 3 pain parameters can be detected while using the CPT: latency to pain onset (threshold in seconds); pain intensity during hand immersion (0-100 on a VAS); and latency to pain intolerability (spontaneous hand removal, defined as pain tolerance in seconds). However, since previous studies have repeatedly demonstrated that OIH is commonly manifested by prolongation of the tolerance to cold pain, we have chosen to use this parameter for evaluation of OIH in the present study as well (14,16,18,25-26).

Evaluation of Clinical Pain

Daily pain reports

Patients received pain diaries in which they were instructed to record the average daily pain intensity during the 4 weeks of the study. Pain was rated each day from 0-100 on a VAS, where 0 represented "no pain" and 100 represented the "worst pain one can imagine." This measurement was regarded as the primary analgesic outcome of the study.

Spontaneous pain relief (%)

Following 4 weeks of treatment, patients were asked to rate their highest percentage of reduction in clinical pain intensity from the baseline while consuming the maximum opioid dosage administered. The question was phrased as follows: "What is the highest percentage of your pain relief compared to your initial pain?"

The Oswestry Disability Index (ODI)

The Hebrew version of the Oswestry Disability Index (ODI), which is a self-administered 10-item questionnaire, was used to evaluate pain and pain-related disability. The first section rates the intensity of pain, and the other sections describe its disabling effect on typical daily activities. The score for each item ranges from 0 to 5, and the sum of the 10 scores is expressed as a percentage of the maximum score, ranging from 0 (no disability) to 100 (maximum disability) (27).

Short-Form McGill Pain Questionnaire (SF-MPQ)

The Hebrew version of the Short-Form McGill Pain Questionnaire (SF-MPQ) was used for a verbal assessment of the different aspects of pain. The main component of the SF-MPQ consists of 15 descriptors (11 sensory, 4 affective), which are each rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective, and total descriptors (28).

Objective Opiate Withdrawal Scale

The Objective Opiate Withdrawal Scale (OOWS) evaluates 13 observable physical signs of opioid withdrawal (e.g., piloerection, lacrimation, and yawning). Each item is rated as either present (score = 1) or absent (score = 0) during the course of 10 minutes (29).

Study Medication

Patients were treated with escalating doses of oral, controlled-release hydromorphone hydrochloride (Jurnista) (Janssen-Cilag, developed by ALZA Corporation, Vacaville, California, USA). The initial daily dose for all patients was 4 mg, and the maximum amount allowed was 24 mg. All dosages were administered as a single dose at bedtime. Dose increments were allowed every fifth day and were based on clinical judgment while taking into account the following considerations: whether adequate analgesia had been achieved (as determined by the patient); whether side effects precluded further titration; and whether a total of 24 mg per day had been reached. Patients who reported constipation following drug administration were instructed to use lactulose (maximum dose 30 cc/d) or bisacodyl (maximum dose 5 mg/day). In case of severe pain during the washout period (see study design section), acetaminophen (maximum dose 3 gr/d) was allowed as a rescue drug. No additional medications or treatments for pain control were allowed.

Study Design

This single-center, open-labeled, prospective study was approved by the Ethics Committee of Rambam Health Care Campus in Haifa, Israel (IRB number 143-10 RMB). Patients who responded to the advertisement in the newspaper were initially screened on the telephone, and eligible patients were subsequently seen for a clinical evaluation. All patients received a detailed explanation about the study medication and procedures. Those who had previously been taking opioids or other analgesics were required to undergo a washout period in order to ensure that they were not consuming any pain medications, apart from rescue doses of acetaminophen (up to 3 gr/d), for at least 72 hours prior to the first (baseline) study session. Patients were instructed to complete the OOWS questionnaire at the beginning of each session. Assessment of the first OOWS was done during the baseline session in order to check that no patients were experiencing opioid withdrawal while the baseline psychophysical tests were being conducted.

Patients were assessed prior to initiation of the hydromorphone hydrochloride (baseline) and after 4 weeks of treatment. Both sessions included the same psychophysical pain tests, which were performed in a fixed order (Fig. 1). At the beginning of each session, patients received a short training session in order to familiarize them with the tasks, the devices, and the perceived sensations. The training tests were not used in the statistical analyses. Ten minutes later, a second round of tests was conducted and counted as the test measurements. Heat and cold pain tests were both conducted on the dominant hand, with heat tested on the

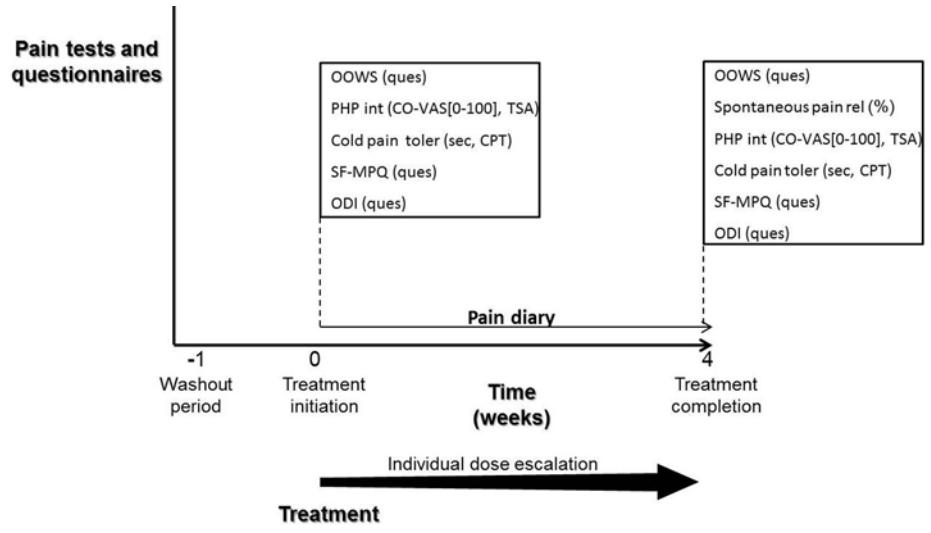

Fig. 1. *An illustration of the study design.*
The study consisted of a washout period followed by a 4-week treatment period with oral hydromorphone hydrochloride. Patients were assessed prior to and following treatment using psychophysical tests and questionnaires.

volar aspect of the forearm and cold by immersing the dominant hand into the cold water bath. All tests were performed by the same investigator, and a 10-minute break was provided between 2 consecutive tests. All tests were performed during morning hours.

Hydromorphone treatment was initiated on the day of the baseline assessment. The titration of hydromorphone was described in the study medication section. In case of intolerable side effects, patients were instructed to return to the previous dosage. Patients were instructed not to change the hydromorphone dosage for at least 3 days prior to the second study session.

In order to rule out possible test-retest variability of the psychophysical test results, a control group of 10 healthy participants underwent 2 identical psychophysical test sessions, 4 weeks apart from each other, without receiving any medications whatsoever.

Statistical Analyses

SPSS software for Windows Version 17 statistical package (SPSS, Inc., Chicago, IL) was employed in the statistical analyses. The change in experimental pain measures was calculated by subtracting the baseline value from the value obtained during the second session. The change in clinical pain measures was calculated by subtracting the value obtained during the second session from the baseline value. The distributions of all variables were examined.

A Shapiro-Wilk W test of normality (Analyse-it, version 2.20, Analyse-it Software Ltd., Leeds, United Kingdom) revealed that both the experimental and clinical pain measures were not normally distributed; hence, all analyses were based on nonparametric tests. Wilcoxon signed rank test was employed to assess the differences in the experimental and the clinical pain measures between both sessions. Spearman's correlations were utilized to assess the correlations between all tested measures and patients' age, gender, or pain duration; the associations between dosage and the changes in all pain parameters (both experimental and clinical), as well as between the experimental and the clinical pain measures. All values are reported as mean ± standard deviation, and significance was considered at the $P < 0.05$ level.

Results

Patients

An a priori power analysis revealed that the required calculated sample size for demonstrating significant correlation between clinical analgesia and experimental hyperalgesia should consist of 27 patients (power [1-β] = 0.8; α error = 0.05; effect size = 0.5). Assuming that about 25% of the patients will drop out from the study during treatment, we intended to initiate therapy in at least 36 patients. Therefore, participation in the study was offered to as many patients as needed in order to allow this number of treatment initiations. Thus, a total of 162 patients were initially considered for participation in the study, including 61 who had previously been treated in Rambam's Institute of Pain Medicine and 101 who had responded to an advertisement in the local newspaper. Of the 52 patients who were found to be clinically eligible, 15 refused to participate in the study for various reasons (e.g., lack of spouse's consent, fear of opioid addiction). Of the 37 patients who were actually enrolled in the study, 7 were unable to complete the study due to a number of reasons (4 patients had either an increase or a lack of improvement in their clinical pain within the first 2 weeks of hydromorphone treatment, one patient had severe constipation, one patient had shortness of breath, and one patient had a brief loss of consciousness). Full recovery from these side effects was reported by all patients shortly after treatment discontinuation. Demographic characteristics and prior treatments are summarized in Table 1.

Table 1. *Patient characteristics*

Patients' Characteristics	Mean±STDEV
Age (years)	47.5± 13.1
Weight (kg)	83.3± 15.9
Gender	**Frequency N (%)**
Female	9 (30%)
Male	21 (70%)
Previous pain treatments	**Frequency N (%)**
NSAIDS/ simple analgesics/physical treatments	19 (64%)
Opioids	3 (10%)
Nerve root block/epidural steroid injection	9 (30%)
Back operation	9 (30%)
Affected nerve root	**Frequency N (%)**
L2	1(3%)
L3	0
L4	4 (13%)
L5	17 (57%)
S1	8 (27%)

Thus, complete data for this study were available from a total of 30 patients, including 21 men and 9 women, ranging in age from 22 to 68 years old with a mean age of 47.5 ± 13.1 years. The mean pain duration prior to study enrollment was 70.2 ± 107.4 months, ranging from 3 to 468 months (with a median of 24 months). In all but one patient, the level of the herniated disc was L4-S1 (Table 1). The 10 healthy control participants consisted of 7 men and 3 women, ranging in age from 27 to 55 years old with a mean age of 35.7 ± 9.2 years. We wish to emphasize that they were recruited solely for the purpose of ruling out possible habituation to the psychophysical tests due to repeatability.

The mean hydromorphone dosage for the entire patient sample was calculated based on the dose reported by each patient at the end of the 4-week treatment period. The mean dose for the entire sample was 11.6 ± 4.8 mg, ranging from 4 to 20 mg with a median of 12 mg.

Opioid withdrawal

As noted in Table 1, 3 patients consumed low doses of opioids (equivalent to 30 mg of oral morphine or less) for pain control, but none of them on a regular basis or during the 14 days prior to entering the study. No evidence for opioid withdrawal was found in either of the 2 study sessions. The OOWS scores at baseline were 0 ± 0 and following the 4-week regimen of hydromorphone treatment were 0.4 ± 0.8.

Evaluation of evoked experimental pain

Phasic heat pain response

The inter-individual change in the intensity of the phasic heat pain response between baseline and the end of treatment was found to vary considerably. Of the 30 patients, an increased heat pain intensity after treatment was found in 17 patients; a decreased heat pain intensity was found in 12 patients; and no change was found in one patient (Fig. 2). Regardless of this heterogeneity, hydromorphone treatment resulted in a significant rise for the entire group, on average, in the intensity of the phasic heat pain response (baseline VAS of 48.2 ± 33.1 versus end of treatment VAS of 60.8 ± 29; $P < 0.05$). This indicates that, overall, hydromorphone treatment led to experimental OIH. In contrast, no significant differences were found for the control group in the intensity of the phasic heat pain response between baseline and the end of week 4 following treatment (32.9 ± 27 versus 33.9 ± 28, respectively; $P = 0.65$), in-

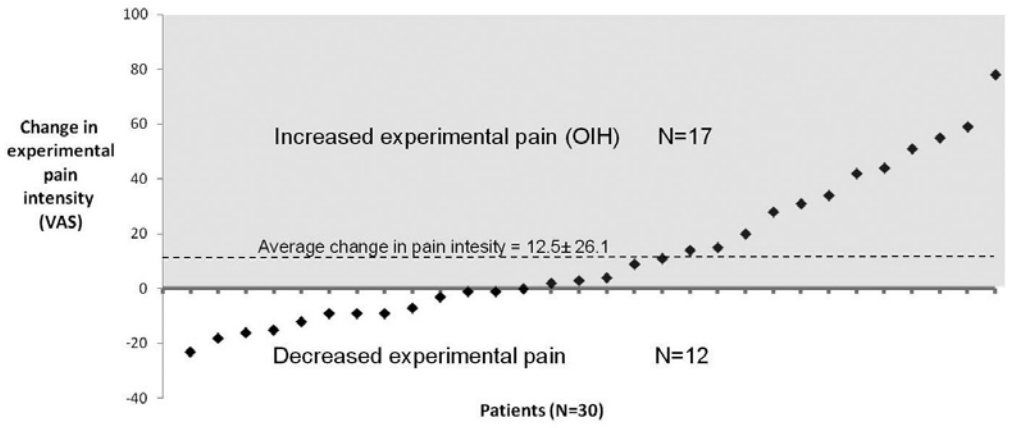

Fig. 2. *Distribution of the changes in intensity of the phasic heat pain response. Each dot represents the change in the intensity of the phasic heat pain response for a particular patient. An increased intensity of the heat pain response following treatment, as compared to baseline, was found in 17 patients; a decreased intensity was found in 12 patients; and no change was found in one patient. The dotted line represents the mean ± standard deviation of the change in the intensity of the phasic heat pain response for the entire group. Notably, patient numbers were assigned according to the magnitude of change in the intensity of the heat pain response.*

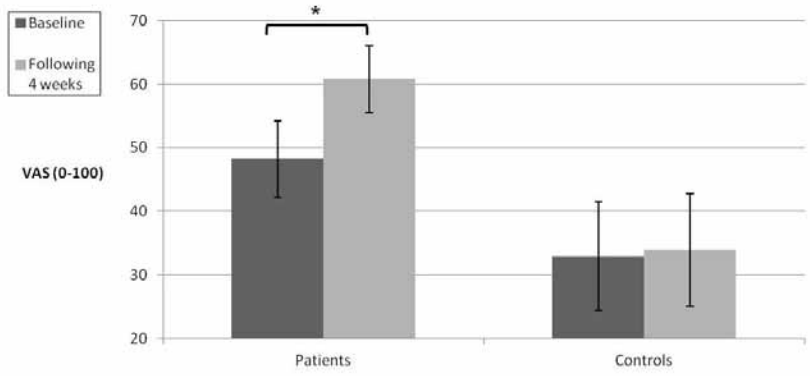

Fig. 3: *Intensity of the phasic heat pain response at baseline and following a 4-week regimen of oral hydromorphone treatment. Intensity of phasic heat pain response at baseline (dark grey) and 4 weeks later (light grey) (following 4 weeks of oral hydromorphone treatment for the patient group). A significant difference was found in the patient group ($P < 0.05$), but not in the control group. Data are presented as mean ± standard deviation.*

Table 2. *Clinical pain measures prior to and following a four-week regimen of oral hydromorphone treatment*

Measure	Baseline	End of treatment	Change from baseline: Mean ±SD (range)	*P* value
Daily pain ratings	64±15.2	38.6±26	25.4±25.8 (-20-70)	$P < 0.001$
Spontaneous pain relief (%)			50.7±33.7 (0-100)	
SF-MPQ sensory	17.2±5.6	9.7±7.3	7.5±6.1 (-3-17)	$P < 0.001$
SF-MPQ affective	4.1±2.5	2.6±2.9	1.5±2.9 (-6-9)	$P < 0.05$
SF-MPQ total	21.3±7.4	12.4±10.1	8.9±8.2 (-5-22)	$P < 0.001$
ODI	43.0±13.4	31.8±17.3	11.2±14.5 (-10-48)	$P < 0.001$

dicating that repeating this test twice, 4 weeks apart, has by itself no effect on the results (Fig. 3). The mean heat pain intensities at baseline differed between the patient and the control groups, though similar differences have been reported in the literature (30-31).

Cold pain tolerance

No significant differences in cold pain tolerance were found between baseline and the end of treatment for either the patients (40.1 ± 41.6 versus 43.9 ± 48.8, respectively; $P = 0.38$) or the controls (27.9 ± 15.8 versus 30 ± 19.5, respectively; $P = 0.44$).

Evaluation of clinical pain

Significant changes were found in all clinical pain measures from baseline to the end of hydromorphone treatment (Table 2). The mean daily pain intensity reports (primary analgesic outcome) dropped by nearly 26 VAS points (range of decline was 20-85 points), from 64 ± 15.2 at baseline to 38.6 ± 26 following treatment ($P < 0.001$). A decreased intensity of the clinical pain following treatment was found in 25 patients; an increased intensity was found in 4 patients; and no change was found in one patient (Fig. 4).

In terms of percentage of pain reduction, the mean spontaneous pain relief reported at the end of treatment was 50.7% ± 33.7%. Similarly, both the sensory and the affective components of the SF-MPQ also significantly declined during the treatment period, together leading to a significant decrease in the total SF-MPQ score (from 21.3 ± 7.4 at baseline to 12.4 ± 10.1 following treatment; $P < 0.001$). In addition, a decrease in pain-induced disability, as measured by the ODI, was demonstrated (from 43.0 ± 13.4 at baseline to 31.8 ±

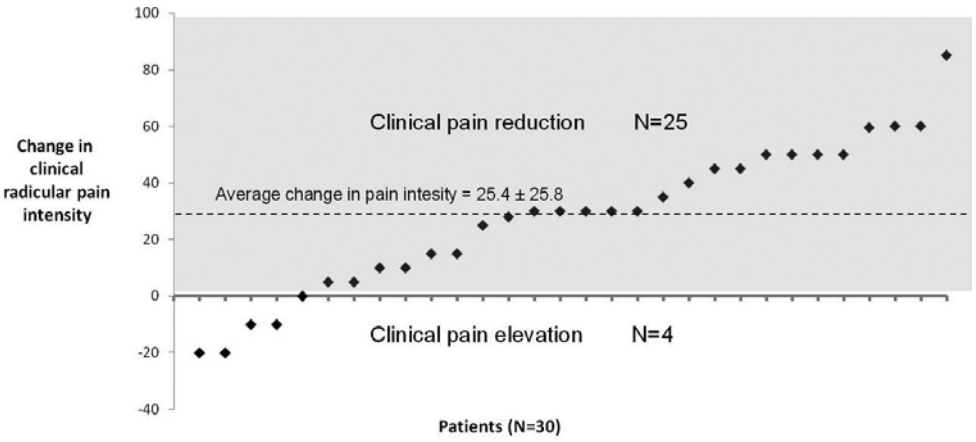

Fig. 4: *Distribution of the daily changes in intensity of the clinical radicular pain (primary analgesic outcome). Each dot represents the change in the intensity of the clinical radicular pain for a particular patient. A decreased intensity of the clinical pain following treatment, as compared to baseline, was found in 25 patients; an increased intensity was found in 4 patients; and no change was found in one patient. The dotted line represents the mean ± standard deviation of the change in the clinical pain intensity for the entire group. Notably, patient numbers were assigned according to the magnitude of change in the clinical pain.*

17.3 following treatment; $P < 0.001$). These findings indicate that under the current experimental conditions, hydromorphone treatment led to clinical analgesia.

Correlations between the change in experimental pain, the change in clinical pain, and the hydromorphone dosage

Significant correlations were found between the hydromorphone dosage, the change in experimental pain (OIH), and the change in clinical pain, meaning opioid-induced analgesia (OIA). Hydromorphone dosage was found to be positively correlated with the change in phasic heat pain intensity (Spearman's test: r = 0.467, $P = 0.009$). In addition, hydromorphone dosage was found to be negatively correlated with the change in daily pain reports (r = -0.592, $P = 0.001$); with spontaneous pain relief (r = -0.442, $P = 0.014$); and with the changes in all questionnaires (ODI: r = -0.429, $P = 0.018$; SF-MPQ total: r = -0.563, P = 0.001; SF-MPQ sensory: r = -0.530, $P = 0.003$; and SF-MPQ affective: r = -0.453, $P = 0.012$). Change in phasic heat pain intensity (OIH) was found to be negatively correlated with the change in daily pain reports (r = -0.389, $P = 0.037$) and with the changes in all questionnaires (ODI: r = -0.423, $P = 0.02$; SF-MPQ total: r = -0.451, $P = 0.012$; SF-MPQ sensory: r = -0.361, $P = 0.050$; and SF-MPQ affective: r = -0.530, $P = 0.003$). In addition, significant correlations were found among the changes in all clinical pain measures. Details of these correlations are presented in Table 3. No significant correlations were found between any of the tested measures and patients' age, gender, or pain duration.

Discussion

The main findings of this preliminary prospective study were: hydromorphone did induce experimental hyperalgesia, as measured by an elevation in the intensity of phasic heat pain response; hydromorphone exhibited an analgesic effect on clinical neuropathic pain, as indicated by a reduction in all clinical pain measures; a significant negative correlation was found between experimental OIH and all clinical pain measures; and hydromorphone dosage was positively correlated with OIH and negatively correlated with its clinical analgesic effect. An illustration of the relationship among hydromorphone dosage, OIH, and OIA is presented in Fig. 5.

Hyperalgesia

Although OIH is frequently mentioned as a potential unwarranted consequence of intermediate-term opioid use, especially in patients with chronic pain, there is only scarce literature which supports its

Table 3. *Correlations between hydromorphone dosage and the change in experimental and clinical pain measures*

	Dose	Δ Phasic heat pain response	Δ Daily pain reports	Δ ODI	Δ SF-MPQ total	Δ SF-MPQ sensory	Δ SF-MPQ affective	Spontaneous pain relief
Dose	1	**0.467****	**-0.592****	**-0.429***	**-0.563****	**-0.530****	**-0.453***	**-0.442***
Δ Phasic heat pain response		1	**-0.389***	**-0.423***	**-0.451***	**-0.361***	**-0.530****	-0.312
Δ Daily pain reports			1	0.500**	0.657***	0.677***	0.439*	0.710***
Δ ODI				1	0.550**	0.523**	0.554**	0.530**
Δ SF-MPQ total					1	0.848***	0.942***	0.655***
Δ SF-MPQ sensory						1	0.692***	0.679***
Δ SF-MPQ affective							1	0.487**
Spontaneous pain relief								1

* <0.05, ** <0.01, *** <0.001. Significant correlations between hydromorphone dosage, OIH and analgesia are highlighted in bold font.

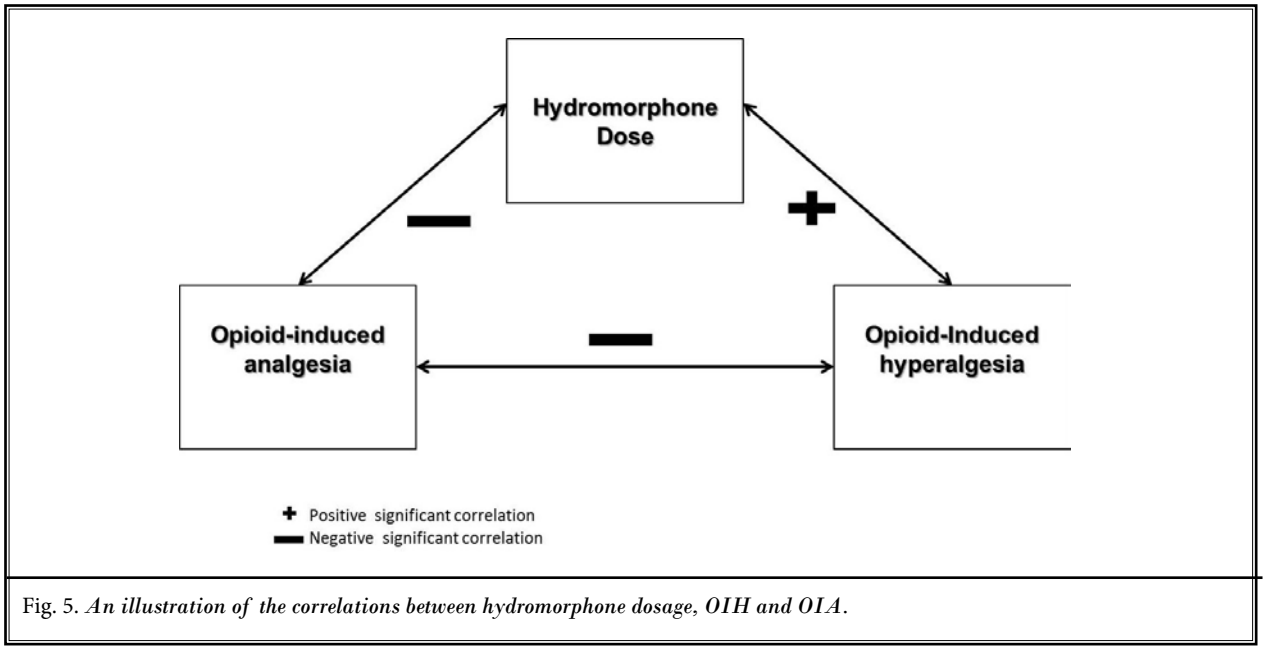

Fig. 5. *An illustration of the correlations between hydromorphone dosage, OIH and OIA.*

occurrence in this clinical setting. To the best of our knowledge, only 2 prospective studies have provided evidence for OIH in patients with chronic pain following intermediate-term opioid treatment. One study that provided indirect evidence for OIH showed an increase in heat pain thresholds from baseline values among patients with chronic pain who were gradually withdrawn from opioid treatment while attending a pain rehabilitation program (23). Another preliminary prospective study, published by Chu et al (18), found hyperalgesia to cold tolerance following one month of morphine treatment in a small sample of 6 patients with chronic low back pain.

The results of our study are somewhat in line with those of the latter study in showing evidence for OIH following one month of oral opioid treatment. However, there are two main differences between the 2 studies that should be emphasized. First, in Chu's study, as well as in others (14,16,26), OIH was demonstrated by measuring tolerance to cold pain, while no evidence for OIH could be demonstrated by evaluating heat pain thresholds. In contrast, no evidence for

OIH was found when testing for cold pain tolerance in our study; rather, the intensity of the phasic heat pain response was the measure through which OIH could be demonstrated. Evidence for OIH measured by heat pain intensity has been found in at least one previous study in healthy participants (32). Unfortunately, although well documented, no clear explanation as to why OIH develops in response to different painful stimuli under various experimental or clinical setting has been suggested so far. Second, Chu et al (18) demonstrated OIH during remifentanil infusions in addition to intermediate-term oral morphine treatment, whereas we found OIH during intermediate-term opioid administration with no additional pharmacological manipulations.

Furthermore, it is worth noting that different models of acute withdrawal from short-term remifentanil infusions have been used in many studies to demonstrate OIH (11,33-35). We believe that our experimental setting, which consisted of individually titrated, intermediate-term hydromorphone therapy with no additional pharmacological interventions, may more accurately represent the phenomenon of OIH in the clinical setting of intermediate-term opioid therapy, especially as no evidence of opioid withdrawal was detected by the OOWS questionnaire. These methodological inconsistencies between studies, as well as the large interpatient variability in the magnitude of OIH found in our study, highlight the importance of establishing a reliable model for OIH in the context of intermediate-term opioid therapy.

Dose-dependent OIH

A positive correlation between opioid dosage and OIH is well documented in animals (7-8,36-38) but to the best of our knowledge, this is the first prospective study to document a development of OIH that significantly and positively correlates with opioid dosage in patients with chronic pain. Similar evidence, although from a different perspective, was provided by Hooten et al (23) who reported a correlation between opioid dosage and OIH, as measured by heat pain thresholds, in a group of 109 patients upon their admission to a multidisciplinary rehabilitation program. Furthermore, they also showed that the tapering of greater morphine equivalent doses resulted in a lower magnitude of OIH at the end of the program.

It might be important to note that both the mean and the maximum opioid doses used in the present study were in the moderate range (mean equivalent to ~80 mg and maximum equivalent to ~140 mg of daily oral morphine while using a hydromorphone: morphine ratio of 1:7) (39). Under these conditions, only 4 of the patients who completed the study developed evidence of clinical OIH. Yet, as previously mentioned, an additional 4 patients were unable to complete the study due to either an increase or a lack of improvement in their radicular pain during hydromorphone administration. Two points seem to emerge from these findings. First, one cannot rule out the possibility that higher opioid doses (i.e., above the equivalent of 200 mg/d) would have resulted in a much more profound clinical and experimental OIH. In such a case, it is possible that clinical OIH would have become apparent in a larger number of patients. Thus, further studies with higher opioid doses are clearly needed. Second, the finding that experimental OIH was revealed in a larger number of patients than clinical OIH (17 versus 8) in the current experimental setting may suggest that experimental OIH is more profoundly demonstrated than clinical OIH. However, this observation awaits further confirmation.

Analgesia

Interestingly, even though lumbar radicular pain is the most common form of neuropathic pain, only a small number of randomized controlled trials (RCTs) have tested the efficacy of different drug treatments for this chronic pain syndrome. Even more interesting is the finding of the only RCT that tested the efficacy of opioids for radicular pain. It showed that oral morphine administered at a daily dose of 15-90 mg resulted in pain reduction which was only 7% superior to that of a placebo (40). Although our study was not designed as an RCT, and its primary goal was not to test the efficacy of hydromorphone in reducing radicular pain, our preliminary results point to a significant reduction of approximately 26 VAS points in the primary analgesic outcome, as well as in all other clinical measures of pain, in response to hydromorphone therapy. It is noteworthy that similar magnitudes of pain reduction are not exceptional in the context of opioid therapy for various neuropathic pain syndromes (41).

It should be noted that the reason for the increase in radicular pain intensity following hydromorphone treatment reported by 4 patients is unclear. It can be attributed to either OIH or worsening of the primary clinical condition regardless of the opioid therapy. Since a distinction between these possible causes cannot be

made, the worsening in pain in those patients was not regarded as a clinical presentation of OIH.

Correlation between opioid dosage and analgesia

Surprisingly, significant negative correlations were found between the individual opioid dosage at the end of treatment and the magnitude of analgesia, as represented by all clinical pain measures. A possible explanation for this finding is that the simultaneous occurrence of a dose-dependent OIH counteracted the OIA.

These negative correlations are in contrast with those of at least one RCT that clearly demonstrated greater analgesia using a high dose of levorphanol as compared to a lower dose of the same drug in a group of patients with mixed forms of neuropathic pain (40). However, there is a profound difference between the 2 studies insofar as the correlations in our study were based on inter-individual dose-response relationships, whereas the correlations in the other study were calculated for the entire group and therefore represent intra-individual dose-response curves. Notably, most of our patients also required dose escalation over the course of the treatment period, meaning that they also likely exhibited normal intra-individual dose-response curves.

Correlations between opioid-induced analgesia and hyperalgesia

Another novel finding that emerged from the present study was the negative correlation between experimental OIH and clinical OIA. Although the experimental OIH was not dominant enough to fully dismiss the analgesic effect, the main practical importance of these relationships is that, for the first time, they point to the clinical significance of experimentally demonstrated OIH in the context of intermediate-term opioid therapy.

Study Limitations

Several limitations of the present study should be emphasized: first, this is an open-labeled study and therefore its results should be regarded as preliminary and interpreted causally until both analgesic and hyperalgesic effects of hydromorphone are demonstrated in future RCTs in similar patient populations. This is particularly important because OIH was demonstrated experimentally by exposing the patients to an acute pain stimulus, but as mentioned earlier, not by worsening of the chronic clinical pain. Only an RCT in which statistically significant worsening of chronic clinical pain in response to an opioid as compared to a placebo can finally validate the fact that clinical OIH indeed develops. Nonetheless, this first report on significant correlation between experimental OIH and clinical OIA is of clinical interest by itself. Second, our control group consisted of healthy volunteers rather than patients who received either placebo or nonopioid treatment. Lastly, although not a direct limitation of the present study, the fact that we have demonstrated OIH while measuring heat pain intensity but not cold pain tolerance while others found the opposite, indicates that the ability to reliably demonstrate OIH has not reached a consensus.

Conclusion

The preliminary findings of the present study suggest that: opioids have the potential to activate both pronociceptive and antinociceptive pathways in a given individual; OIH and OIA act in a counterbalancing manner such that if one is more dominant, the other is less apparent; it might be possible that the effects of opioids on pronociceptive and antinociceptive systems may share common mechanisms, though this is still far from being understood and requires further study; and if indeed verified in future studies, the correlation between OIH and OIA may help identify patients who are susceptible to having a poor response to opioid treatment.

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