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Aims and Scope

The European Journal of Pain is the journal of the European Federation of Chapters of the International Association for the Study of Pain (EFIC). It is a multi-disciplinary journal that aims to be a global forum on all aspects of pain and its management. The journal differs from existing pain journals in its clinical and educational emphasis. The journal publishes clinical and basic science research papers relevant to all aspects of pain and its management, including specialties such as anaesthesia, dentistry, neurology and neurosurgery, orthopaedics, palliative care, pharmacology, physiology, psychiatry, psychology and rehabilitation; socio-economic aspects of pain are also covered.

The journal publishes original clinical and basic science articles; reviews on pertinent topics not recently covered by other international journals; clinical and experimental notes; case reports of educational or scientific value, qualified and long-term clinical observations, technical advances in clinical practice and experimental research, therapeutic studies or experiments with negative results and pain-provoking procedures; short communications on clinical or basic science articles; and letters to the Editor. The journal will also include the following commissioned articles: invited commentaries; tutorials with questions and answers; mini-reviews updated by a board of specific editors. A bulletin board will notify about new scientific and therapeutic developments, relevant issues of other publications, and major meetings. European Training Programmes etc.

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Editorial

This issue completes the Journal's 4th volume as well as the mandate of the first Editorial Board. Those who attended the Pain in Europe III Congress in Nice last September will already know that Professor Fernando Cervero, who has served as Deputy Editor from the start of the Journal, is taking over as Editor-in-Chief. He will provide excellent leadership in this position and the Journal as well as EFIC is to be congratulated on this choice. Professor Cervero has already appointed a new Editorial Board which is published in this issue. As you will notice, Professor Harald Breivik is the new Deputy Editor and the board at large has a new and more functional structure. Another new feature is that the Editorial Office has been moved from London to Professor Cervero's office at the University of Alcalá in Madrid. We are confident that these changes will facilitate communication with authors and reviewers and help to reduce publication delays.

I take the occasion of writing this editorial to include a short historical note on the Journal. When EFIC was constituted during the 7th World Congress on Pain in Paris in 1993, the idea was to foster the aims of IASP in Europe by collaboration between its Chapters. The publication of a new pain journal was discussed as one of the possible endeavours of EFIC. After further discussions, the Council of EFIC decided at its meeting in Verona in 1995 to launch a high quality international journal to be published by an established publisher. I accepted the appointment as Editor-in-Chief in May 1996 and selected an Editorial Board of distinguished scientists and clinicians, most of whom were from Europe, but some also from overseas to emphasize the international character of the Journal. A few months later the current publisher was contracted by the Executive Board of EFIC, and the aims and scope of the Journal were announced internationally. An office with a dedicated editorial assistant connected to the publishing house was established in London. The first issue was published in March 1997 and the editorial service was successively developed further, along with the publisher's marketing for subscriptions etc. The Belgian and Swiss Chapters were the first to take advantage of the option of bulk subscriptions at a reduced price. Importantly, the Journal is currently being indexed by international databases including Medline and we are looking forward to receiving the first ISI impact factor in 2001. The published articles are increasingly being cited and we are enjoying a steady submission rate of about 100 original articles annually. The Journal's website has been developed to serve the scientific as well as the clinical communities and we are looking at a continued success with further expansion of the Journal.

Finally, on a personal note as outgoing Editor-in-Chief, for me the editorship has been an exciting as well as a demanding task, which of course has been dependent upon the active contributions from many authors in different pain related disciplines who submitted high quality manuscripts. The vast majority of the articles have come from Europe. I have also greatly appreciated the invaluable professional support with the review process of submitted material by the members of the Editorial Board and many other colleagues.

Ulf Lindblom
FOUNDBING EDITOR
Relationship between mechanical sensitivity and postamputation pain: a prospective study

Lone Nikolajsen\textsuperscript{a,b}, Susanne Ilkjær\textsuperscript{b} and Troels S. Jensen\textsuperscript{a,c}

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Limb amputation is followed by stump and phantom pain in a large proportion of amputees and postamputation pain may be associated with signs of hyperexcitability such as hyperalgesia to mechanical stimulation. The present study examined the possible relationship between mechanical pain threshold of the limb and early (after 1 week) and late (after 6 months) phantom pain. Thirty-five patients scheduled for amputation of the lower limb were examined before, 1 week and 6 months after amputation. On all three examination days pressure–pain thresholds were measured and compared with the simultaneous recording of ongoing pain intensity assessed on a visual analogue scale (VAS). There was a weak but significant inverse relationship between preamputation thresholds and early stump and phantom pain. There was no relationship between preamputation thresholds and late stump and phantom pain. One week after amputation there was a significant and inverse relationship between mechanical thresholds and phantom pain but no relationship was found after 6 months. The findings suggest that although tenderness of the limb before and after amputation is related to early stump and phantom pain, the relationship is weak. Neuronal sensitization peripherally or centrally may play a role in the development of phantom pain. © 2000 European Federation of Chapters of the International Association for the Study of Pain

KEYWORDS: phantom pain, stump pain, preamputation pain, mechanical hyperalgesia.

INTRODUCTION

Limb amputation is followed by stump and phantom pain in the majority of patients (Jensen \textit{et al.}, 1985; Nikolajsen \textit{et al.}, 1997a), yet the underlying mechanisms are still unclear. Following nerve transection, previous studies have shown that a number of changes occur both peripherally and more centrally in the nervous system (Coderre and Katz, 1997; Woolf and Mannion, 1999). Ectopic output from both sensitized severed nerve endings, including organized neurones (Wall and Gutnick, 1974), and from dorsal root ganglion cells (Wall and Devor, 1983; Kajander \textit{et al.}, 1992) may induce sensitization of spinal dorsal horn neurons (Woolf 1983; Woolf and Mannion 1999). The clinical manifestations of such sensitization is not known in detail but may include reduction of pain threshold (hyperalgesia), evocation of pain by non-noxious stimuli (allodynia) and pain evoked by repetitive pricking stimuli (wind-up-like pain) (Coderre and Katz, 1997; Woolf and Mannion, 1999).

There are also indications in amputees that noxious input from the periphery before, during and after amputation may play a role for stump and phantom pain. It has been shown that preamputation pain increases the risk of postamputation stump and phantom pain (Jensen \textit{et al.}, 1985) and that a high intensity of preamputation pain is related to a high intensity of early postamputation pain (Nikolajsen \textit{et al.}, 1997a). Case
reports have shown a striking resemblance between phantom pain and pain experienced before the amputation (Katz and Melzack, 1990; Hill et al., 1996). In addition, wind-up phenomena by repetitive stimulation of the stump elicited phantom pain (Carlen et al., 1978; Nikolajsen et al., 1996).

More direct evidence that the periphery could be a generator and a site for maintaining stump or phantom pain came from microneurography studies. Nyström and Hagbarth (1981) observed abnormal activity in peroneal and median nerve fibres of two amputees with ongoing pain in their phantom foot and hand, respectively. Tapping neuromas in these two patients increased discharges in afferent fibres and accentuated their phantom pain. Chabal et al. (1989) injected gallamine (a potassium channel blocker), lidocaine and saline into the stump of nine amputees. Gallamine increased pain, lidocaine decreased pain and saline had no effect.

There are also indications that central sensitization could contribute to phantom pain. Nikolajsen et al. (1996) demonstrated wind-up-like pain in a group of amputees with phantom pain. Following a N-methyl-D-aspartate (NMDA) receptor antagonist (ketamine), with a presumed effect spinally (Gottrup et al., 2000a, 2000b), wind-up-like pain and phantom pain were reduced. Phantom pain is also associated with changes in the somatosensory cortex. Flor et al. (1998) described a reorganization of cerebral cortex in amputees with pain and Birbaumer et al. (1997) found that a brachial plexus blockade abolished pain and reorganization in three out of six amputees. There is therefore both experimental and clinical evidence that sensitization peripherally and/or centrally can play a role for development and persistence of phantom pain. We addressed this issue in a prospective study in which we looked at the possible relationship between limb sensitivity to mechanical stimuli and the intensity of early and late postamputation pain.

PATIENTS AND METHODS

Patients

Patients were recruited from a major trial in which 60 patients scheduled to undergo amputation of a lower limb at the Department of Orthopaedic Surgery, Aarhus University Hospital, during a 25-month period from August 1994 to August 1996, were randomized to receive either epidural or conventional analgesia before the amputation. Amputations were carried out under general anaesthesia and postoperative pain was treated with epidural bupivacaine and morphine. Exclusion criteria were: dementia, acute amputation, ipsilateral reamputation and contraindications to epidural catheters or a combined epidural and general anaesthesia. The two treatment groups (epidural versus conventional treatment before the amputation) were combined in the present study because the preoperative epidural treatment showed no beneficial effect on postamputation pain (Nikolajsen et al., 1997b) or stump sensation (Nikolajsen et al., 1998).

Informed written consent was obtained from all patients and approval was obtained from the local Ethics Committee and the Danish National Board of Health.

Pain assessment

Pain assessment was carried out using a visual analogue scale (VAS, 0–100 mm). On the day before amputation, pain intensity in the limb was recorded. One week and 6 months after the amputation, intensity of stump pain (defined as pain localized to the stump) and phantom pain (defined as pain in the missing part of the limb) were recorded.

Sensory testing

Pressure–pain threshold (PPT) was determined using a hand-held electronic pressure algometer (Somedic AB, Sweden). Briefly, a circular probe with an area of 1 cm² was used and the pressure application rate was 20 kPa/s. In order to minimize comprehension problems in this group of mainly older patients they were asked to say 'stop' when a sensation of pressure changed to a sensation of pain. At this point the examiner activated a push button and the applied pressure in kPa was frozen on the digital display of the algometer. Each PPT value was determined three times with
FIG. 2. Regression plot of pressure pain thresholds after amputation and stump (left panel) and phantom (right panel) pain 1 week (upper row) and 6 months (lower row) after amputation. Each dot represents one patient; n = 23 (1 week) and n = 18 (6 months).

DISCUSSION

Sensitization before amputation and postamputation pain

This study prospectively addresses the issue of hyperexcitability as a source of pain in patients with nerve injury. The main objective of the study was to examine whether sensitization before amputation implies a risk for subsequent development of stump and phantom pain. We found a weak inverse relationship between limb pain threshold before amputation and early, but not late postamputation pain. These findings lend support to much experimental literature that states that sensitization of the nervous system before a nerve injury implies a risk for subsequent development of postinjury pain. In
animal models of neuropathic pain it has been shown that noxious stimulation of the paw or the sciatic nerve in the rat before neurectomy significantly shortens the onset of autotomy and enhances its severity (Dennis and Melzack, 1979; Seltzer et al., 1991; Katz et al., 1991).

Pretreating animals with NMDA receptor antagonists such as MK-801 can prevent hyperalgesia following nerve injury (Woolf and Thompson, 1991; Mao et al., 1993). While these findings clearly suggest that preinjury pain is associated with a risk of postinjury pain there is only limited (if any) prospective clinical support in humans for the notion that longlasting pain induces secondary changes in the nervous system which persist after a nerve injury and predict the development of postinjury pain. However, indirect support is obtained from case reports that pain experienced before amputation may persist or recur as phantom pain (i.e. a painful ulcer which continues to be present in the phantom) (Nathan, 1962; Katz and Melzack, 1990; Hill et al., 1996). We have previously shown that intense preamputation pain is more likely to be followed by intense postamputation stump and phantom pain (Jensen et al., 1985; Nikolajsen et al., 1997a).

The present weak relationship between pain threshold before amputation and early postamputation pain with no relationship 6 months after amputation suggests that other mechanisms than preamputation pain and sensitization play a role in subsequent postamputation pain. The failure to observe a relationship between preamputation pain threshold and late (6 months) postamputation pain may, of course, reflect the small number of patients examined. We would note, however, that the lack of relationship is matched by a similar lack of relationship between clinical preamputation intensity and late stump and phantom pain (Nikolajsen et al., 1997a).

We failed to find a relationship between preamputation PPT and preamputation pain intensity. The small number of patients examined may play a role in this lack of relationship. However, the finding is similar to that found in other studies that pain threshold in the individual patient is not matched by current ongoing pain. Taken together, preamputation pain is probably determined by several different factors.

**SENSITIZATION AFTER AMPUTATION AND POSTAMPUTATION PAIN**

Following a peripheral nerve injury, increased spontaneous and evoked activity can be recorded from severed nerve endings (Wall and Gutnick, 1974; Devor and Seltzer, 1999) and from cell bodies in dorsal root ganglia cells (DRGs) (Wall and Devor, 1983). In addition to increased peripheral excitability, enhanced spontaneous and evoked activity can also be recorded in the dorsal horn of the spinal cord. Increased neuronal responses, prolonged afterdischarges, expansion of receptive fields and recruitment of new responding cells are some of the findings observed in the dorsal horn following a nerve injury (Palecek et al., 1992; Laird and Bennett, 1993). Abnormal neuronal activity can also be recorded at higher levels such as the dorsal column nuclei, thalamus and cortex both in animals and humans (Guilbaud et al., 1990; 1992; Lenz et al., 1998; Davis et al., 1998). Thus a peripheral nerve injury induces hyperexcitability changes that extend from the periphery, DRG, spinal cord and brainstem to several cortical structures. It may therefore be difficult to determine the origin of a hyperexcitability which manifests itself in lowered thresholds.

In the present study there was a relationship between mechanical pain threshold and early, but not late, postamputation pain. Again, the relationship was weak after amputation. These findings thus suggest that other factors than hyperexcitability with lowered mechanical threshold in the stump may influence and predict the development of pain. As indicated above, a series of events occur following nerve injury which involve both the peripheral and the central nervous system. A more clear picture may have emerged if a larger group of patients without postamputation pain were included in the study.

**Sources of error**

There are several possible sources of error in a study like this such as small numbers, medication, insufficient pain assessment and site of threshold measurement.

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Pressure–pain threshold measurement was only carried out in a limited number of patients, who otherwise participated in a randomized trial (Nikolajsen et al., 1997b) so it is possible that the inverse relationship between limb sensitivity and pain is due to a biased selection of patients. Although we cannot dismiss this possibility, we consider it less likely as baseline characteristics for patients who underwent sensory testing and those who did not participate in sensory testing were similar (unpublished observations).

The medication patients were offered before and after amputation may also have influenced the present results. Before amputation, patients were almost all treated with opioids and peripheral acting analgesics. Since patients were their own control and had a mean VAS score of 54 before amputation it is unlikely that analgesics were responsible for the present findings. In addition, a previous study showed that an intensive epidural blockade with morphine and bupivacaine had no effect on postoperative mechanical and thermal thresholds in this group of patients (Nikolajsen et al., 1998).

The pain measures used in the present study were simple: pain intensity and mechanical pain threshold. The VAS score was chosen as the most simple measure for the experienced pain intensity. We cannot exclude the possibility that the inclusion of other parameters such as pain descriptors and McGill Pain Questionnaire may have provided other findings. However, we would note that our previous study showed that these three measures changed in the same direction (Nikolajsen et al., 1997a).

Pain threshold to mechanical pressure was chosen to assess sensitization. This is an indirect measure and it is possible that a more systematic search for neuromas might have picked up sites of sensitization. Previous studies have shown stumps and neuromas to be particularly susceptible to mechanical pressure and not to other stimuli, for example thermal (Nystrom and Hagbarth, 1981; Nikolajsen et al., 1996; Devor and Seltzer, 1999). Pain threshold could, for obvious reasons, not be measured at exactly the same site before and after the amputation. Care was taken, however, to carry out threshold measurements at the same site (approximately 5 cm from the cutting line on the limb). The failure to find a clear relationship between pain threshold of the stump and late phantom pain may also indicate that sensitization be it peripheral or central, has a short-lived effect as a determinant for persistent stump and phantom pain. Taken together, we cannot dismiss the possibility that several of the above factors may have influenced the results. Further studies in amputees with and without phantom pain are needed to determine whether the clear experimental evidence for sensitization is matched by similar findings in the clinic, perhaps by including other stimulus modalities.

CONCLUSION

The present prospective study found a relationship between mechanical sensitivity of the limb before and after amputation and early experienced postamputation pain. These findings are compatible with the theory that neuronal sensitization peripherally and/or centrally contributes to postamputation pain.

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REFERENCES


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Does failure hurt? The effects of failure feedback on pain report, pain tolerance and pain avoidance

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In this study an experiment was conducted to examine whether failure experiences have an effect on pain report, pain tolerance and pain avoidance. Furthermore, it was investigated if negative affectivity (NA) affected the impact of failure feedback on pain report, either as a mediator, in the case of negative state affect, or as a moderator when NA as a personality trait was considered. Fifty-four healthy female volunteers were included and randomly assigned to one of three conditions: (1) failure feedback; (2) success feedback; (3) neutral control task. After the manipulation, subjects were given a cold pressor task in order to obtain pain measures. Regarding the effects of failure feedback on pain report, it was found that, in comparison with success feedback, failure feedback led to increased pain report. With regard to pain tolerance, pain was tolerated for longer when preceded by success feedback than when preceded by failure feedback. Differences between failure and control conditions did not reach significance. With regard to pain avoidance, no differences between the conditions were found. The hypothesized mediating role of negative state affect was not found. Though in the hypothesized direction, no significant effect was found for NA-trait moderating the influence of failure on pain. The discussion focuses on a number of research questions that remain to be answered, and the clinical relevance of the effects of failure and success experiences on pain report and pain tolerance. © 2000 European Federation of Chapters of the International Association for the Study of Pain

KEYWORDS: pain report, pain tolerance, pain avoidance, failure feedback, negative affectivity.

INTRODUCTION

Common cerebral processes, involved in both emotion and pain, suggest that the experience of pain is always modulated to some extent by co-existing emotions (Melzack and Wall, 1965; Robinson and Riley, 1999). Because of this, it might not always be clear how both constructs relate to each other. Some studies support the hypothesis that negative emotion is a frequent psychological reaction to pain, i.e. emotional distress is a consequence of both acute and chronic pain (Craig, 1994; Gamsa, 1990). This study focuses on mechanisms by which emotions may instigate or increase pain. Although there is no empirical support for the proposition that emotional distress really causes pain (Gamsa, 1994), there is sufficient evidence that pain
can be moderated by distress. Sternbach (1986) observed that stressful events, including major life events or daily life 'hassles', are strongly associated with increased pain. It can also be hypothesized that the influence of a stressor is mediated by a negative emotional state, such as depression or anxiety. Depressive states have been shown to increase clinical pain in humans (Brown, 1990; Sullivan and D'Eon, 1990; Wade et al., 1990), and to decrease tolerance for experimentally induced pain (Zelman et al., 1991; Romano and Turner, 1985). As for anxiety states, there is no clear empirical basis for the proposition that anxiety increases pain. A review of studies by Arntz et al. (1991) indicated that anxiety might enhance or relieve pain, or not affect it at all. Their review concluded that anxiety has no unequivocal effect on pain, but that the anxiety–pain relationship is mediated by attention. With regard to positive mood states, there is some evidence which suggests that positive emotional states, induced by imagery or self-controlled distraction, enhance pain tolerance (Horan and Dellinger, 1974; Chaves and Barber, 1974; Zillmann et al., 1996). Evidently, the effect of emotional mood states on pain depends on different dimensions, such as attention paid to the stressor, mood quality and mood intensity. Moreover, ecological validity of the kind of mood inductions used in experimental studies might be of influence.

Failure experiences can be an important source of emotional distress and therefore directly or indirectly influence pain. Levine et al. (1993) examined whether experience of pain can be influenced by a mental stressor and by the perceived failure or success in dealing with this non-pain-related stressor. Two dimensions of the experimental situation were manipulated: task difficulty and feedback quality (failure or success).

Undergraduate students were randomly assigned to one of five conditions: an easy reading comprehension task with either success or failure feedback; a difficult reading comprehension task with either success or failure feedback; or a control condition. After false success or failure feedback was given in the comprehension task conditions, a cold pressor test was conducted. Subjects were asked to place their non-dominant hand in a bucket of circulating ice water, 0-2°C, up to their wrists, for a maximum of 2 min. During immersion in the cold pressor, subjects were asked to score their pain intensity every 30 s. In this experiment, feedback turned out to be more important than task difficulty in the explanation of pain report. Failure feedback led to higher pain reports than a non-feedback control condition. Success feedback, on the other hand, did not lead to a decrease of pain report as compared to a control condition (Levine et al., 1993).

A number of methodological aspects, however, may weaken the conclusion of this study. First, the impact of the manipulation was not checked, so it remains unclear whether the manipulation succeeded. In particular, the absence of effects of success feedback may have resulted from the manipulation not being strong enough. Second, it was not clear from this report whether the same experimenter executed both the comprehension task/control task and the cold pressor task. If so, the experimenter was not blind for the condition. A third note concerns the pain measure. In order to prevent ceiling effects, subjects in the Levine study were told that they could choose numbers higher than the maximum of the scale (32). No word-anchors were given above 32, therefore, it becomes unclear what pain subjects were experiencing if their pain was rated worse than excruciating (>32). A fourth remark could be made about the way ratings were coded after withdrawal from the cold pressor: all ratings beyond tolerance time were assigned a rating of 64. When defined like this, the pain intensity measure is likely to be confounded with pain tolerance.

Besides these methodological aspects, there are three theoretical issues that are of interest: the comparison between failure and success condition, the role of negative affectivity (NA), and the effect of perceived failure on behavioural aspects of pain. Even though the success condition did not lead to a significantly lower pain report than the control condition, the largest contrast may be expected to be between failure and success. It therefore might be interesting to compare these conditions directly.
In their discussion, Levine et al. (1993) proposed that NA might at least partly have accounted for the effect of failure on pain report. Watson and Clark (1984) originally described the NA construct as a mood dispositional dimension or trait. High-NA individuals tend to be distressed and have a negative view of themselves. Moreover, high-NA individuals are more prone to experiencing significant levels of distress and dissatisfaction at all times and in any given situation. High-NA individuals are more introspective and differentially dwell on their failures and shortcomings (Watson and Pennebaker, 1989). Thus, when failure was perceived in the Levine et al. study, an NA disposition (NA-trait) could have moderated the effect of failure on pain report, because high-NA individuals were more sensitive to the failure feedback. According to Watson and Pennebaker (1989) NA can also be an induced state, and it is quite possible that failure feedback induced such a negative emotional mood state (NA-state). This emotional state might have mediated between failure feedback (the stressor) and increased pain reports, or at least may have been partly responsible for increased pain reports in the failure condition. Hence, two different roles of NA can be hypothesized: as a moderator when referring to an NA-trait, or as a mediator when referring to an induced mood state (Baron and Kenny, 1986).

It would be worthwhile investigating whether, besides subjective pain report, behavioural aspects of pain (pain tolerance and avoidance) are also affected by antecedent failure experiences. Moreover, measurement of pain behaviour would provide a more objective outcome measure. In addition to the Levine replication, we therefore add the following research questions: are pain-related activities, when preceded by negative feedback, i.e., failure, less well tolerated or more avoided?

In summary, the aim of this study was to determine the effects of failure and success experiences on pain report, pain tolerance and pain avoidance. Furthermore, with regard to NA, the following question was examined: does NA influence the effect of failure on pain report, either as a mediator (NA-state) or as a moderator (NA-trait)? There were a few methodological modifications in comparison with the original study of Levine et al.: (a) a manipulation check was included; (b) the intelligence test and cold pressor task were performed by two different experimenters, with the second experimenter being blind to the condition; (c) to prevent subjects from becoming demotivated and reluctant during the experiment in which they were told they had failed an intelligence test, manipulation and cold pressor task were presented as two independent studies; (d) the maximum score on the pain intensity scale was kept at 32.

METHODS

Subjects

Sixty-three first-year undergraduate students were recruited by means of posters at different faculties of the Maastricht University. The advertisement was designed such that subjects were led to believe that they were being invited for two independent experiments. The first would be a pencil and paper task. The second would be a laboratory experiment investigating the influence of pain and emotion on skin conductance levels (SCL). In case the subject asked how pain would be inflicted, he or she was told that this was by immersion of the hand in cold water. The candidates were told that they could decide themselves when to stop the test. Because only six male students were recruited and because it was not feasible to recruit equal numbers of male and female subjects to both conditions within the time, we decided to include only female students. Fifty-four of the 57 female students met the inclusion criteria (blood pressure lower than 140/90 mmHg; no medical contraindications, no analgesics used within the last 12 h). Two subjects were excluded because of medical reasons (blood pressure above 140/90; did not feel well) and one subject was excluded because her housemate disclosed the rationale of the experiment to her. The remaining 54 subjects had a mean age of 19.1 (range: 18–22 years).
Measures

**Manipulation check.** The manipulation check consisted of a 0 to 100-percentile expectancy-scale. The subject was asked to indicate the expected percentile score on the intelligence test when she compared herself to a pre-university reference group. The scale was completed twice: before starting the intelligence test, and immediately after the manipulated feedback was given. On the second occasion, the subject was asked to give expectancy-scores with regard to completion of a similar test in the near future. Besides this check, two additional Visual Analog Scales (0–100) were used just before final debriefing. On these scales, the subject could indicate how disconcerted she was about the feedback given, and how satisfied she was about the test results, respectively. Both questions were checked to identify those subjects who were not disconcerted at all despite unsatisfying test results. In cases where unsatisfying results did not seem to disconcert the subject, the experimenter questioned the subject in order to find out the reason. If the subject declared that she was not disconcerted because she did not believe the test results, the manipulation had failed and the subject was deleted from the analyses.

**Pain intensity and unpleasantness.** During the cold pressor task, pain intensity and pain unpleasantness were both rated by means of two 32-point rating scales (Padawer and Levine, 1992). Pain words used in the original scales were translated into Dutch and checked. The scales were scored every 30 s with a pencil held in the subject’s non-immersed hand. Scales were presented in a booklet, each page containing one pain intensity and one pain unpleasantness scale. Subjects were asked to turn the page immediately after scoring such that new scales became visible.

**Pain tolerance.** Pain tolerance was defined as the time elapsed (in s) between immersion and withdrawal from the cold pressor. *A priori*, it was decided that the maximum tolerance time was set at 5 min.

**Pain avoidance.** Pain avoidance was recorded as the time elapsed (in s) between final instructions after withdrawal from the cold pressor and the second immersion into the cold pressor.

**Negative affectivity-trait (NA-trait).** NA-trait was measured with the Dutch translation of the Negative Emotionality subscale (NEM) of the Multidimensional Personality Questionnaire (Tellegen et al., 1989; Stegen, 1998). The NEM was taken before the experimental manipulation.

**Negative affectivity-state (NA-state).** NA-state was measured by the Dutch translation of the shortened version of the Profile Of Mood States (POMS, Wald et al., 1990). The POMS has been shown to be a valid and responsive measure of negative affect. McNair (1971) reported effects on the POMS in the hypothesized direction with regard to short-term psychotherapies, drug trials and mood-inducing conditions. Because of high correlations among three subscales of the POMS (tension, anger and depression), they were joined into one composite measure. This composite measure was further used in this study. NA-state was measured twice, first before the manipulation task and before the measurement of NA-trait, and second just before the cold pressor task, after the manipulation.

**Procedure**

**Failure manipulation.** Subjects were randomly assigned to one of three conditions: (a) an intelligence test with failure feedback; (b) an intelligence test with success feedback; or (c) an ‘evaluation of art’ control task. Experimenter 1 conducted the manipulation, and was therefore informed about the randomization scheme. After blood pressure had been measured and the medical condition checked, two informed consent forms were signed, one for each experiment. After completion of the POMS and the NEM scales, instructions about the test were provided.

In the intelligence test conditions, the subject was told that the test was being conducted as a pilot for national implementation. The intelligence test was said to give a valid indication of
her scientific qualities and would be applied as an entrance exam for university. After a brief introduction, the expectancy-scale (manipulation check) was administered, followed by the intelligence test. It consisted of 24 selected items of the ‘Drenth Series’ (Drenth et al., 1965, 1969 and 1970), an intelligence test developed to differentiate among subjects with elevated intellectual levels. To maximize failure experiences, six of 24 items were made unsolvable in the failure condition only. In addition, subjects in this condition were given only 25 min to complete the test, whereas in the success condition, subjects had 35 min to complete the test. In order to keep the second experimenter blind for the condition, a filler task of 10 min was given in the failure condition to make experiment duration comparable.

When the subject finished the test, the experimenter immediately entered data into a computer program, after which the manipulated score appeared on the screen. In the failure condition the experimenter reported a fictitious and low percentile score (range: 21st to 28th percentile). It was made clear to the student that the score was very low in comparison with other pre-university students, and the experimenter gave several comments stressing the personal failure. In the success condition, the subject was given a fictitious high percentile score (range: 91st to 98th percentile), together with a couple of reinforcing comments, stressing the extremely favourable performance in comparison with other pre-university students. In both conditions the experimenter checked the scores to convince the student that there was no mistake with data input and processing. Next, a computer printout was given to the student stating ‘Compared to the norms of a reference group of pre-university students...’, followed by the predetermined percentile score. The score forms as well as the forms used for the manipulation check were all given some official coating to make the feedback as credible as possible. Immediately after the feedback, the student was asked to complete the expectancy-scale once more (see manipulation check).

In the control condition the student was requested to give her opinion about abstract pictures, to tell something about her personal taste of art, and to select some favorite paintings out of several artbooks. It was stressed that there was no evaluating purpose in the test, and that it was one’s personal evaluation that mattered. After completion of the manipulation (intelligence test or control task), the first experimenter thanked the student for her participation and handed her directly over to the second (blind) experimenter who waited for her in the laboratory.

**Cold pressor task.** After completing the POMS for the second time, the subject was told that this experiment aimed at investigating the influence of pain and mood on skin conductance levels. Subsequently, and after the attachment of sham SCL-electrodes, a cold pressor task was conducted. The subject was asked to place the non-dominant hand up to the wrist in the cold pressor apparatus. This apparatus consisted of a container filled with ice water, 0–2°C, circulated by a fish-tank aerator. The experimenter scooped out the ice to prevent contact with the subjects’ skin. Water temperature was recorded for each subject before the cold pressor task, but could not be read by the subject. The subject was instructed to tolerate the cold pressor as long as possible. During immersion, the subject was given an audible signal every 30 s to rate pain intensity and unpleasantness on a 32-point rating scale. When the hand was withdrawn from the cold pressor, the tolerance time was clocked and an audiotape instructed the subject to complete both scales once more for the pain she felt just before she withdrew her hand from the cold pressor. After a few seconds, new audiotaped instructions were given to restart the same cold pressor task once more when the subject felt ready for it. As soon as the subject reimmersed her hand into the cold pressor, the avoidance time (the time the subject delayed reimmersing her hand) was clocked. The subject was now told she could withdraw from the cold pressor and that the task was finished. The cold pressor task was executed by means of the Micro Experimental Laboratory Professional software package (Schneider, 1988).

Immediately after the cold pressor task, the experimenter asked what kind of test was carried out in the preceding experiment. When this was an intelligence test, the experimenter requested
the subject to complete the two VAS-scales designed as two additional manipulation check measures. Finally, the subject was debriefed.

Hypotheses

The following hypotheses were put forward: (1) in the failure condition, subjects report higher pain intensity ratings than subjects in the control condition (replication Levine et al., 1993), and than subjects in the success condition; (2) subjects in the failure condition tolerate the cold pressor for a shorter period of time than subjects in the control condition, and than subjects in the success condition; (3) subjects in the failure condition avoid immersing their hand in the cold pressor a second time for a longer period of time than subjects in the control condition, and than subjects in the success condition; (4) NA-state mediates between failure feedback and pain report; (5) NA-trait moderates the effect of failure on reported pain intensity; high NA-subjects are more prone than low NA-subjects to react with high pain reports in a failure condition.

Statistical analyses

To test Hypothesis 1, repeated measures MANOVA on the successive pain ratings was conducted. As in the original study, only pain ratings at a 60-, 90- and 120-s interval (measurement) were taken into analyses. The highest rating on the scale (32) was assigned to ratings when the subject’s hand was withdrawn from the cold pressor. Though the procedures were identical to those in the Levine et al. study, we used a score of 32 instead of 64, for reasons named in the introduction. As differences were expected between the failure vs control and the failure vs success condition, but not between success vs control condition, post-hoc planned comparisons between all three conditions were performed. An ANOVA and post-hoc planned one-tailed t-tests for independent observations were conducted for testing hypotheses 2 and 3. Because it was hypothesized that tolerance time was positively correlated with avoidance time, tolerance time was taken into analyses as a covariate, when analysing pain avoidance.

To construct a hypothetical model for the role of NA-trait and NA-state in reported pain intensity, multiple linear regression analyses were conducted. Statistical analyses were carried out according to Baron and Kenny (1986). To test for mediation, three regression equations were tested (Baron and Kenny, 1986): (1) regressing the mediator (NA-state) on the independent variable (condition); (2) regressing the dependent variable (pain report) on the independent variable (condition); (3) regressing the dependent variable (pain report) on both the independent variable (condition) and the mediator (NA-state). To establish mediation, the effect of the independent variable on the dependent variable should be less in the third regression equation than in the second (Baron and Kenny, 1986). Besides condition, NA-trait and NA-state (premanipulation) were added to the first regression equation, and NA-trait was added to the second and third regression equations.

To test hypothesis 5, the product of condition and NA-trait was added to the regression equation. The moderator effect is indicated by the significant effect of the interaction while predictor and moderator variables are controlled (Baron and Kenny, 1986). With regard to hypotheses 4 and 5, pain reports on the 120-s time interval were taken into analysis and the last reported score was assigned when the subject had already withdrawn her hand from the cold pressor. The hypothetical model is presented in Figure 1.

![Diagram](https://via.placeholder.com/150)

FIG. 1. The hypothetical model.

*European Journal of Pain (2000).*
RESULTS

Manipulation check

As expected, the pre-post expectancy-scores increased by 27.39 percentiles in the success condition, whereas a decrease of 27.44 was found in the failure condition. This difference was significant (t(34) = -14.19, p < 0.001). Furthermore, subjects (Ss) in the failure condition were significantly more disconcerted about the intelligence test feedback than Ss in the success condition (t(33) = 10.59, p < 0.001), whereas Ss in the success condition were significantly more satisfied about their results than Ss with failure feedback (t(33) = -17.02, p < 0.001). Only one subject reported not to be disconcerted despite unsatisfying test-results. However, she did not doubt the genuineness of the test-score, but attributed the bad score to a temporary state (a hangover) instead. It was therefore decided to keep the data of this subject in the analyses. Finally, it was checked if failure induced negative affect. Change scores pointed out that failure Ss increased NA-state, whereas success Ss decreased NA-state (t(19.36) = 3.38, p < 0.003). In summary, experimental manipulation appeared to be successful.

Pain report

Reported pain intensity ratings over four time-intervals are shown in Figure 2. The pain unpleasantness measure significantly correlated with the pain intensity measure (r > 0.90; p < 0.001, for each of the 60-, 90- and 120-s time-intervals), and results were identical for both measures. Therefore, as in the Levine et al. study, only the results of the pain intensity measure are presented. Because pain report was not normally distributed, scores were reflected (maximum score +1 minus observed pain intensity score) and transformed (square root). Means and standard deviations after transformation can be found in Table 1. Due to the reflection of data before transformation, highest scores become lowest and lowest become highest. Repeated measures MANOVA (measurement X feedback condition) was conducted with 'Measurement' as the within-subjects factor with three levels: pain report at 60, 90 and 120s. There was a significant effect for measurement (F(2, 102) = 16.16; p = 0.000), which means that pain report increased as a function of immersion time. Neither condition effect (F(2, 51) = 1.68; p = 0.196), nor measurement X condition interaction (F(4, 102) = 0.63; p = 0.645) reached significance. As planned, post-hoc pairwise comparisons were done. Unlike the original study, only a trend was found with regard to

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain report (VAS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-s</td>
<td>F</td>
<td>2.75</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>3.24</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>3.39</td>
</tr>
<tr>
<td>90-s</td>
<td>F</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2.88</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>2.99</td>
</tr>
<tr>
<td>120-s</td>
<td>F</td>
<td>1.95</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2.74</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>2.96</td>
</tr>
<tr>
<td>Pain tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>120.84</td>
<td>88.89</td>
</tr>
<tr>
<td>C</td>
<td>160.32</td>
<td>103.94</td>
</tr>
<tr>
<td>S</td>
<td>178.49</td>
<td>112.05</td>
</tr>
<tr>
<td>Pain avoidance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>51.12</td>
<td>59.62</td>
</tr>
<tr>
<td>C</td>
<td>35.22</td>
<td>32.57</td>
</tr>
<tr>
<td>S</td>
<td>46.59</td>
<td>46.89</td>
</tr>
</tbody>
</table>

n=18 for each condition. F = Failure condition; C= Control condition; S = Success condition.

FIG. 2. Pain intensity ratings over four 30-s time intervals, for each condition.

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comparison of failure and control conditions (estimated difference = -0.64; SE = 0.462; one-tailed p = 0.086). As in the original study, there was no significant difference between success and control conditions. The additional comparison of failure and success conditions resulted in a significant effect (estimated difference = -0.80; SE = 0.462; one-tailed p = 0.045), which means that during a 60-, 90- and 120-s interval, subjects in the failure condition reported higher pain than subjects in a success condition.

Pain tolerance

Means and standard deviations of pain tolerance (in s) are displayed in Table 1. Subjects in the failure condition, on average, withdrew their hand from the cold pressor almost 1 min earlier than subjects in the success condition. ANOVA showed no statistically significant differences between the three conditions (F(2,53) = 1.501; p = 0.233). Post-hoc planned pairwise comparisons, however, reached significance for the difference between failure and success conditions (t(34) = -1.71, one-tailed p = 0.048). The difference between failure and control conditions was not significant (t(34) = -1.22, one-tailed p = 0.115). Figure 3 shows the number of subjects (per condition) who withstood the cold pressor task. The number of subjects continuing to do so is given for every 30 s.

Pain avoidance

Table 1 gives means and standard deviations of pain avoidance (in s). No differences were found between the conditions (F(2,53) = 0.248; p = 0.781). Pairwise comparisons did not reach significance either (failure vs success: t(34) = 0.161, one-tailed p = 0.437; failure vs control: t(34) = 0.686, one-tailed p = 0.249). Analyses were performed after data transformation (square root). The outcomes of the ANCOVA were comparable to those acquired when tolerance time was not taken into analysis as a covariate.

The mediating role of NA-state

To test the hypothesized mediating role of NA-state, three multiple regression analyses were performed. One subject was left out of the analyses because the score on negative affect (post-manipulation) was identified as an outlier. Final results of the regression analyses are presented in Table 2. To simplify interpretation of reflected and transformed data, the original direction of the relationship as expressed in the Standardized Beta was restored. The Variance Inflation Factors were small enough (range 1.01–1.74), which suggests that there is no problem of collinearity. First, predictors of NA-state (post-manipulation; mediator) were analysed. A model was entered with NA-trait, NA-state (pre-manipulation) and condition (failure vs control/success) as predictors of NA-state (post-manipulation; Table 2, model 1). The model predicted 58% of the variance and feedback condition was one of the predictors. Secondly, the predictive value of feedback condition on pain report was tested (Table 2, model 2). Results showed that this was not the case, and therefore the mediation hypothesis was rejected. Nonetheless, the third analysis, in which the mediator was added to the regression equation, is reported because, in contrast to the second equation, condition significantly predicted pain report in this equation (Table 2, model 3a). Although accounting for only 13% of the variance, the third equation, with NA-trait, condition (failure vs control/success) and NA-state (post-manipulation) as predictors, was
TABLE 2. Regression analyses of NA-state (post-manipulation) and pain report.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>N</th>
<th>Adj. R²</th>
<th>Explatory variables</th>
<th>Standardized Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) NA-state (post-</td>
<td>53</td>
<td>0.581***</td>
<td>1) NA-state (pre-manipulation) 0.518***</td>
<td></td>
</tr>
<tr>
<td>manipulation)</td>
<td></td>
<td></td>
<td>NA-trait 0.304**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Condition (failure vs success and control) 0.438***</td>
<td></td>
</tr>
<tr>
<td>2) Pain report</td>
<td>53</td>
<td>-0.009</td>
<td>2) NA-trait 0.097</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Condition (failure vs success and control) 0.141</td>
<td></td>
</tr>
<tr>
<td>3a) Pain report</td>
<td>53</td>
<td>0.132*</td>
<td>3a) NA-state (post-manipulation) 0.492**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA-trait 0.331*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Condition (failure vs success and control) 0.325*</td>
<td></td>
</tr>
<tr>
<td>3b) Pain report</td>
<td>53</td>
<td>0.158*</td>
<td>3b) NA-state (post-manipulation) 0.571**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA-trait 0.496**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Condition (failure vs success and control) 0.364*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interaction: NA-trait x condition 0.248</td>
<td></td>
</tr>
</tbody>
</table>

Analyses 1 to 3a refer to the test of the mediator effect of NA-state; Analysis 3b refers to the test of the moderator effect of NA-trait. ***p<0.001; **p<0.01; *p<0.05.

significant. Surprisingly, in the third equation, NA-state contributed to the predictive model of pain report, but in the opposite direction: the higher NA-state (post-manipulation), the lower the pain report. Rather than mediating the effect of failure on pain report, NA-state seemed to confound the effect. Only by controlling for it, the predictive model, in which condition was one of the predictors, became significant.

The moderating role of NA-trait

With regard to the moderator effect, the interaction term (NA-trait X condition) was added to the third model (Table 2, model 3b). Although the Beta coefficient appears to be in the expected direction, the interaction term did not reach significance. Hence, it cannot be concluded that there was a moderator effect of NA on pain report.

DISCUSSION

After successful manipulation of success and failure feedback, this study showed that, compared to success, failure leads to increased pain report and decreased pain tolerance during a cold pressor test. However, differences between failure and control conditions, which reached significance in the Levine et al. study, did not reach significance in the current study. Although findings were in line with the original study, they only partly supported the ‘failure hurts’ hypothesis: in a female student population, pain report was increased only when failure was compared to success feedback, not when compared to a control condition. Furthermore, in contrast to what Levine et al. (1993) proposed, we did not find evidence for the mediating role of NA-state in the failure-pain report association. Neither did we find support for the moderator effect of NA-trait on the influence of failure experiences on
pain report, although results point in the hypothesized direction.

One of the reasons for the weaker support might be the methodology used. First, in the Levine-study subjects were told that they could choose ratings higher than the maximum of 32 to prevent ceiling effects. This could have increased differences, especially when those subjects who already scored high on the rating scale used this option. A second methodological difference is the way missing ratings were recoded. In the original study, after withdrawal from the cold pressor, ratings were recoded with the value of 64, whereas in our study the maximum value on the pain intensity scale was used (i.e. 32). Recoding missing values (after withdrawal from the cold pressor) as 64 may have increased the mean pain report in the condition where subjects withdrew their hand early and tolerated less. Unfortunately, Levine et al. (1993) did not report for which conditions the 25 missing ratings were recoded, but based on our tolerance data, it is likely that missings occurred mostly in the failure condition.

Another reason why significance levels differ between the two studies might be the impact of the manipulation. Although the manipulation check in our study proved that the feedback manipulation was successful, the manipulation in the Levine et al. study could have been more powerful because of non-specific factors such as impact of the experimenter or the verbal feedback given with the computer output. In general, it might be difficult to find an experimental false feedback manipulation that is strong enough to impress subjects, and is also ethically acceptable.

Another possibility is that the art control task could have led to unnoticed feelings of frustration and ‘failure’ if subjects were not interested in or ignorant of art. This could have hampered the intended contrast between both conditions.

Not only pain report was influenced by failure feedback, we also found that failure tolerance was influenced. This would suggest that, as compared to success conditions, pain-eliciting activities are more likely to be quitted earlier as a result of failure in non-pain related domains. So far, pain tolerance has been reported to be influenced by psychological variables, such as pain-related fear (Vlaeyen et al., 1995), dissociative tendencies (Orbach, 1994), pain-incompatible imagery (Neumann et al., 1997), distraction, and even humour and laughter (Weisenberg et al., 1995). Furthermore, Keefe et al. (1997) found that in arthritis pain, self-efficacy relates positively to pain tolerance in experimental pain. In our study there are some indications that failure experience might be an additional determinant of pain tolerance. Pain tolerance has clinical importance in that reduced tolerance may generalize to daily activities of which the reduction leads to increased disability levels in chronic pain patients. The role of non-pain-related failure experiences in the development and maintenance of chronic pain deserves further examination.

With regard to pain avoidance, the expected effect was not found. This is surprising, because from literature on learning foundations (Kanfer and Philips, 1970) one would expect that processes (i.e. aversive stimulation) influencing avoidance would be comparable to those influencing tolerance. On the other hand, in a study by Cipher and Fernandez (1997) it was found that expected pain tolerance significantly predicted actual tolerance, whereas expected danger significantly predicted pain avoidance. These findings suggest that pain avoidance and pain tolerance might not have the same predictors. As we decided to operationalize pain avoidance by the time subjects delayed the start of a second cold pressor task, this measure is likely to be influenced by the preceding cold pressor task, which might have biased results on pain avoidance. Tolerance time, pain on stopping the first task and anticipation of pain, are likely sources of variance with regard to the moment subjects decide to immerse their hands into the cold water a second time. Furthermore, based on the previous task, subjects may have decided to start the next one soon, but to withdraw their hand quickly, whereas others, avoid longer as to prepare for another long immersion time. It therefore seems more prudent to examine the effects of failure feedback on tolerance and avoidance in separate experimental set-ups.

The mediating role of NA-state was not confirmed. In contrast, the regression analysis pointed in the opposite direction, which raises new questions. Analysis of the separate regressions within
each condition reveals that the negative relation between NA-state and pain report only holds for
the control condition. In both feedback condi-
tions, no relation was found between NA-state
and pain report. There are no clear explanations
for these findings. It still remains an interesting
question which factors could possibly mediate
between failure feedback and pain report. We
suggest that attributional processes might be one
of the alternative possibilities: Whether failure is
attributed internally (‘It’s my fault’) or externally
(‘I’m not responsible for this failure’), stable and
global (‘always and on any occasion’) or unstable
and specific (‘just today on this particular task’),
is likely to make the difference. Mikulincer
(1986), for example, found that performance in a
dissimilar situation was impaired when failure
(unsolvable problems) was attributed to global
and stable causes, and when it was attributed to
global and internal causes. In a later study, it was
found that exposure to unsolvable problems
worsened subsequent performance only when
subjects attributed failure to stable causes
(Mikulincer, 1988). Likewise, Klein et al. (1976)
found that only the failure that leads to decreased
belief in personal competence is sufficient to pro-
duce helplessness deficits in men. Whether attri-
butional style rather than NA mediates the
effects of failure to pain report and pain behav-
ior, might be a topic for future research.

There was no evidence for the moderating role
of NA-trait. Still, it might be of interest to investi-
gate whether negative effects of failure feedback
might be attributed to the absence or presence of
specific traits. Relevant in this respect might be a
comparable experiment by Ciota et al. (1998),
which found that self-esteem modulated the in-
fluence of feedback on pain in that low self-esteem
plus negative feedback participants reported the
highest levels of pain during a cold pressor task.
In line with this finding it seems very plausible
that sortlike traits such as NA-trait have com-
parable outcomes.

What is the external validity of this study? The
reader is reminded that only female subjects were
included which might have hampered compari-
son with the Levine study. In a study by Riley
(1998), a meta-analysis was carried out on sex dif-
ferences in the perception of noxious experimental
stimuli. They concluded that females are more
pain-sensitive than males. In case of induced
thermal pain, the effect was smaller and more
variable. It might be interesting to compare pre-
diction models for males and females in future
research. At present, it remains unclear whether
the findings are comparable between the sexes.
Our prudent conclusions should therefore be
restricted to female populations.

It would be worthwhile to study the effects of
failure in chronic pain patients especially because
this group might have been confronted with their
own shortcomings and disability for a longer
period of time. Responding to (non-pain-related)
failure experiences with pain behaviour may have
become a habitual way of coping. We are cur-
rently investigating these hypotheses in chronic
low back pain patients (Van den Hout et al., sub-
mitted). If failure indeed holds pain patients in a
vicious circle of trying, failing and avoiding in
future situations, prevention of and dealing with
failure experiences may be of interest in the man-
agement of chronic pain.

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Do epidemiological results replicate? The prevalence and health-economic consequences of neck and back pain in the general population

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Current estimates of the prevalence and consequences of neck and back pain vary greatly between studies. It is not known whether this variance is due to differences in methodology, or if it depends on the dynamics of the problem over time. The aim of this study was consequently an attempt to replicate and extend the findings of a previous epidemiological study using the same methodology on a new population. A survey of 3000 25-45 year olds, selected at random, was conducted to determine the prevalence, site, frequency and intensity of the pain as well as any work loss or health-care utilization. The response rate was 69% and an analysis of non-responders showed that they were very similar to responders, but had a slightly lower prevalence. The results replicated the original study: 73% reported back pain during the past year and the consequences included considerable suffering and functional impairment. Moreover, 17% of those reporting pain had utilized sick leave during the past year for the problem, while an additional 14% had been off work but had not used sick leave. Sufferers averaged 3.5 health-care visits during the past year. However, the consumption of resources was highly skewed and about 6% of the sufferers accounted for over 50% of the costs. It was concluded that when the same selection criteria and assessment techniques are employed, the results found are quite similar. This implies that much of the huge variation in reported prevalence rates and consequences of back pain may be due to methodological differences. This underscores the need for standardized methods.

KEYWORDS: back pain, neck pain, prevalence, health-care utilization, costs, economics.

INTRODUCTION

The epidemiology of back pain might be characterized as a loose collection of studies with varying objectives, designs, populations, definitions of the problem, and measurement techniques. It is not surprising then, that despite the fairly large number of surveys, reports of the prevalence of back pain range from 5 to 85% of the population depending on the study (Andersson, 1991; Frymoyer & Cats-Baril, 1991; Skovron, 1992; Leboeuf-Yde & Lauritsen, 1995; Crombie et al., 1999). A review (Leboeuf-Yde & Lauritsen, 1995) of 26 Nordic studies found that the methodological quality was generally low. For example, these studies used different definitions of pain, various pain sites, and formulations of the question often involving considerably different time spans. Consequently, the present authors point to the difficulties in comparing studies as well as determining the accurate prevalence or incidence rates. It is important to have stable methodology in order to determine, for example, whether the increased costs for back pain are due to an increase in back pain or an increase in health-care use. Therefore, replication, that is repeating a study, is an important objective.

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However, only one attempt at replication was located. This study (Leino et al., 1994) selected 5000 Finnish residents each year, over a 15-year period, and asked them the same question to determine the (point/1-year/lifetime) prevalence of back pain. They found a surprisingly consistent prevalence rate that was almost exactly the same for males and females. Although this is comforting, there is still a need to replicate findings and the Leino investigation was limited to only the prevalence data.

This study focuses on a replication of an epidemiological investigation of neck and back pain, and its consequences. Recently, 3000 35–45-year-olds were surveyed in middle Sweden in an attempt to establish the 1-year prevalence of spinal disorders, as well as the consequences of this pain (Linton et al., 1998). It was found that 66% reported suffering neck or back pain during the previous year. In addition, 19% reported being on sick leave for their pain, and the average sufferer consulted professional help three times during the year. The aim of this study was to attempt to replicate and expand the findings of the authors’ earlier report in a new population that was similarly defined, and employing the same basic questions. Thus, the prevalence and site of the pain are reported, as well as work loss, suffering and health-care utilization. The study design follows the recommendations outlined for such studies (Lebocuf-Yde & Lauritsen, 1995).

METHODS

Overview

This survey was designed as a replication and extension of that by Linton et al. (1998). Therefore, the same selection criteria and questionnaire were employed. Briefly, 3000 people selected at random were surveyed concerning their experience of spinal pain and its consequences on their health, activity, work and health-care use.

Participants

One thousand five hundred people between 35 and 45 years of age were selected at random from each of two communities in the Swedish county of Södermanland. Randomization was done by a third party (Sema Group Infodata). The two communities were Eskilstuna, a semirural industrial city of 117,454 people (total number of 35–45 year olds = 14,200), and Nyköping, a rural town of some 80,070 inhabitants (total number of 35–45 year olds = 7600) with small companies in a variety of branches. These communities are considered to be representative of the county and are located in middle Sweden.

The County Council’s Board on Research Ethics approved this study.

Procedure

The postal questionnaire contained 10 items, took less than 10 min to complete and is described in detail elsewhere (Linton et al., 1998). The main question was ‘Have you suffered from back or neck pain during the past 12 months?’, which is similar to a number of formulations reported in the literature (Svensson & Andersson, 1982; Bierring-Sorensen & Hilden, 1984; Lloyd et al., 1986; Croft et al., 1996). The intention of the question was to identify people who had suffered from pain from the spinal area during the previous year. If the answer to the above question was ‘no’, the individual was asked only to complete background questions concerning their work status (employed, unemployed, student) and gender. If the answer to the main question was ‘yes’, the person was instructed to complete the entire questionnaire including the background questions.

The items concerning the extent of the problem dealt with the site of the pain, pain intensity and number of episodes, function, time off work, and health-care utilization. The site of the pain was ascertained with a drawing indicating the definition of the sites and a ‘yes/no’ checklist for responses. The experience of pain was measured using ‘average’ and ‘worst’ pain during the past 12 months on 0–10-point scales, with 0 representing ‘no pain’ and 10 representing ‘unbearable pain’. Episodes were measured on a category scale (1–3 episodes, 4–10 episodes, more than 10 episodes, continual pain) during the same time period.
Sick leave was ascertained with ‘How many days have you been on sick leave for your neck or back pain during the past 12 months?’, which has been found to be reliable (Keefe et al., 1992; Leboeuf-Yde & Lauritsen, 1995; Linton et al., 1995), where subjects respond by checking the appropriate category. To establish the rate of unofficial absenteeism, subjects were asked ‘Have you missed work because of your back or neck pain without being on sick leave (such as taking vacation, flex-time, care of sick child) during the past 12 months?’, and participants responded with a ‘yes’ or ‘no’. Finally, it was asked ‘When you experience back or neck pain, to what extent does it hinder you from your normal activities or movements?’ (Turk & Melzack, 1992). Participants made a rating from 0 to 10 where 0 was ‘no hindrance’ and 10 was ‘a great hindrance’.

Health-care use was assessed with the question ‘During the past 12 months, how many times have you visited a health-care professional for your back or neck pain?’ (Keefe et al., 1992; Linton et al., 1992). Participants checked the appropriate number from 0 to more than 10 visits for each of the following categories: doctors, physical therapists, specialists and others (e.g. chiropractor, healing).

A packet was sent that contained the questionnaire, information about the project, instructions for completing the questionnaire and a prepaid return envelope. If the questionnaire was not returned, a reminder was sent after 2 weeks and another after 4 weeks.

Statistical analyses

A series of analyses were done to summarize the findings and determine whether they replicated the original study. Employing the same basic design and data analysis allows for direct comparison of the findings with the previous investigation.

The first phase determined prevalence rates and assessed the impact of non-responders. This was done with descriptive statistics.

The second phase evaluated the extent of the problem and the utilization of services. This was primarily done with cross tabulations so that rates specific to a given population could be presented.

The third phase compared the results from the present study with the previous investigation to determine the degree of replication. This was mainly done by examining descriptive statistics.

RESULTS

Participation rate

Of the 3000 mailed questionnaires, 22 people could not complete them (12 did not know Swedish, five had moved abroad, five had prohibitive handicaps) and 197 were not properly delivered to the addressee (i.e. 190 moved, seven were delivered to another person). These cases were eliminated leaving 2781 potential participants. Of those, 1914 (69%) participated in the survey.

Analysis of non-responders (n = 867). Since it is possible that those not completing the survey differ from the respondents, an analysis of non-responders was made. Background data for gender, age and community of residence were compared to investigate if there were any systematic differences. The response rate for the two communities was identical (69%:69%) suggesting that no systematic bias existed for that variable. In addition, about one-half of the responders were women (52.5%) indicating that gender was not a discriminating factor between responders and non-responders. The average age for both responders and non-responders was the same (40 years old). These statistics mirror the selection criteria and suggest that there was no response bias for community, gender or age.

A random sample of non-responders was listed and 50 of these were telephoned. Candidates were asked to respond to the main question in the study, i.e. whether they had experienced back or neck pain during the past 12 months. The prevalence rate for these ‘non-responders’ was 56%, which is considerably lower than the 72% rate for the responders described in detail below. Thus, estimates of the prevalence of
spinal pain in the general public need to take into consideration this discrepancy.

Prevalence

The prevalence of spinal pain is illustrated in Table 1. Of the responders, 72.3% said that they had suffered spinal pain during the past year. The rate is similar for men and women, although about 4% more women than men report pain. However, in addition to the difference between responders and non-responders noted above, there was a more pronounced gender difference concerning the site of the pain. Figure 1 illustrates that women had a higher rate of neck and

<table>
<thead>
<tr>
<th>TABLE 1. An overview of the prevalence of pain from the spinal region during the previous year for 35-45 year-olds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Total responders</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Community</td>
</tr>
<tr>
<td>Eskilstuna</td>
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<td>Nyköping</td>
</tr>
</tbody>
</table>

FIG. 1. The prevalence of men and women reporting pain from various sites.

<table>
<thead>
<tr>
<th>TABLE 2. The rated severity of the pain problem for those suffering pain from the spinal region during the previous year.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Mean pain intensity (0–10 scale)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Community</td>
</tr>
<tr>
<td>Eskilstuna</td>
</tr>
<tr>
<td>Nyköping</td>
</tr>
<tr>
<td>Worst pain intensity (0–10 scale)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Community</td>
</tr>
<tr>
<td>Eskilstuna</td>
</tr>
<tr>
<td>Nyköping</td>
</tr>
<tr>
<td>Functional hindrance (0–10 scale)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Community</td>
</tr>
<tr>
<td>Eskilstuna</td>
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<tr>
<td>Nyköping</td>
</tr>
</tbody>
</table>
shoulder pain relative to men. There was little difference between the rates in the two communities. Consequently, this variable was not included in further data analyses.

Problem severity

Table 2 shows self-reported pain intensity ratings for those reporting an episode of spinal pain during the previous year. The median rating for usual pain, 4.0, was the same regardless of gender or community. Worst pain produced a median rating of 7.0. In fact, 48% reported that their worst pain was 7 or more. While 31% of those with pain reported 1–3 episodes, 43% reported more than 10 episodes or constant pain.

Functional impairment is another measure of problem severity shown in Table 2. For those reporting pain, the median rating for functional impairment was 4.0, which suggests a moderate amount of impairment. However, 48% reported difficulties at 5 or above, and 28% reported impairment as 7 or more.

Work loss

Seventeen percent of those reporting spinal pain said that they had taken sick leave during the previous year. The duration of sick leave tended to be short, but 8% of those reporting pain did have accumulated sick leave of 15 or more days during the last year, illustrating that a small number of sufferers account for a significant amount of the sick leave. In addition to the official sick leave, 14% reported being off work without being sick listed (men = 16%; women = 11%).

Health-care utilization

The average number of self-reported health-care visits during the previous year for those who reported pain is presented in Table 3. In all, the median number of visits per person was 3.5, with women reporting more visits (median = 4.0) than men (median = 3.2). The most frequently visited source of treatment was physical therapists, while alternative medicine was a close second.

The distribution of health-care consumption is graphically depicted in Figure 2. This shows a highly skewed distribution where a relatively small number of people account for a large number of the total visits. In fact, 6% of the sufferers accounted for 50% of the health-care consumption.

![Cumulative visits vs cumulative suffers (%)](image)

**FIG. 2.** The distribution of health-care consumption, shown as the cumulative number of visits, by the cumulative percent of spinal pain sufferers. Note the skewness of the curve as over 50% have no reported visits while a few percent consume the majority of visits.
TABLE 4. An overview of the main results of Linton et al. (1998) and the present study illustrating the degree of replication.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linton et al. (1998)</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (%)</td>
<td>79.5</td>
<td>69</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>66</td>
<td>73</td>
</tr>
<tr>
<td>Non-responders</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>Pain intensity (median, 0–10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Worst</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Pain episodes (&gt;10)</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Functional hindrance (median, 0–10)</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Health-care use (median number of visits)</td>
<td>3.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Work loss (% yes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Official</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Unofficial</td>
<td>15</td>
<td>14</td>
</tr>
</tbody>
</table>

An obvious question is whether those consuming large amounts of health care are the same people as those consuming sick leave. There was a moderate correlation of 0.48 (p < 0.0001) between sick-leave duration and health-care use. As an example of this relationship, those with more than 20 health-care visits were compared with those reporting one to five visits. For the former group (20 visits), 50% had reported more than 90 days of work loss, while for the latter group, less than 1% reported 90 days of sick leave.

Degree of replication

Table 4 provides an overview of the main variables from the present study and the investigation it was meant to replicate. Although the response rate was 4% higher in the original study, the results of the current study replicate the original findings. The 1-year prevalence rate differed by only 7% and ratings of pain intensity, episodes and impairment were virtually the same (on average). In addition, the data concerning work loss and health-care utilization are quite similar.

DISCUSSION

Spinal pain among 35–45 year olds is very common and frequently results in suffering as well as health-care visits and work loss. Moreover, a relatively small number of the sufferers consume a large amount of the resources. The results of this study replicate a previous study surprisingly well. Consequently, the results are quite stable and highlight the need for effective early interventions to reduce suffering and costs. One implication is that the methodological differences in epidemiological studies may account for a substantial amount of the variation found in the results between investigations.

This study demonstrates that when the same population, selection criteria, and assessment methods are employed, the results are remarkably stable. A general population sample from a similar geographic region was employed, and the exact same selection criteria as the study we attempted to replicate were used in the present study. Moreover, the same questions were asked to assess the prevalence of pain and the consequences of it. For most variables, the results were virtually identical. For example, the 1-year prevalence rate in the initial study was 66%, while in the current investigation it was 73%. This difference is deemed to be small given the high frequency (the difference is only 8% of the highest score). This suggests that much of the variation reported in the literature is due to differences in methodology such as selection of the population and assessment techniques. Indeed, Leino has also reported very stable prevalence rates over a 15-year period when the same population, selection criteria, and questions were used (Leino et al., 1994). This underscores the need to improve the methodology in

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epidemiological studies, as well as to develop appropriate measures that may be used in different research settings.

Despite the many similarities, there were slight differences in the populations of the original study and the replication reported here. Although both investigations employed samples from the general population in middle Sweden, they represent different counties. In addition, the replication occurred 2 years after the original study and this time period included some marked economic changes in the area, such as increased unemployment. Such differences in the sample might be expected to produce small differences in the results. Consequently, the measurement error inherent in the assessment technique may be relatively small.

The present findings also underscore the fact that most people can expect to suffer from spinal pain. This sample included people from 35 to 45 years old in the general population, and found that nearly three-quarters reported such pain during the previous year. This means that neck and back pain are difficult to avoid.

The degree of suffering and the consequences of the pain confirm that, on average, a bout of neck or back pain is frequently disabling. The authors were not able to control for possible response biases or scaling behaviour. However, pain at its worst was rated as fairly intense (7 on a 0–10 scale), and the pain tended to recur frequently with most sufferers reporting several episodes or ongoing pain during the year. Moreover, participants attributed marked problems in participating in physical activities to the pain. These findings may be compared to follow-up studies in primary care that also demonstrate that the pain tends to be relatively intense, re-occurs frequently, and results in disability (Linton & Halldén, 1997; van den Hoogen et al., 1997, 1998; von Korff, 1999). Thus, although neck and back pain may be seen as a common occurrence, there is no doubt that it causes considerable problems.

Although extensive suffering was reported, most people managed their pain with little health-care use or work loss, but a small group did account for a large part of the costs. Despite the high ratings of pain at its worst, only 17% of the sufferers said that they had called in sick at their work. In addition, more than half reported no health-care visits whatsoever. However, a small group of about 5% of the sufferers did use large amounts of the resources consumed. This replicates earlier findings and highlights the fact that preventing a problem for a small number of people could produce considerable economic savings (Reid et al., 1997).

Taken as a whole, the results demonstrate the large number of people experiencing spinal pain, the marked suffering involved, as well as the rather high costs. This study replicated earlier findings and suggests that these data are relatively stable. Better early interventions might reduce the suffering and ensuing disability. Indeed, identifying and preventing the development of a problem for the small number who consume most of the resources should be quite attractive for patient and provider.

ACKNOWLEDGEMENTS

Sincere appreciation is expressed to Lotta Wahlström and Ing-Liss Bryngelsson for their expert help in analysing the data and to FIN-SAM Sörmland for their support.

REFERENCES


The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study

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Craighavon Area Hospital Group Trust, Craigavon, Northern Ireland.

The aim of this study was to assess if the pain of osteoarthritis is reduced by topical capsaicin and to determine whether addition of glyceryl trinitrate has an effect on analgesic efficacy and tolerability of capsaicin. A randomized, double blind, placebo controlled study was carried out on 200 adult patients attending a Pain Clinic with osteoarthritis pain. Patients applied one of four creams topically over the affected joint over a 6 week period. Creams contained either placebo (vehicle), 0.025% capsaicin, 1.33% glyceryl trinitrate or 0.025% capsaicin + 1.33% glyceryl trinitrate. Analgesic efficacy, tolerability of cream and analgesic consumption were assessed. One hundred and sixty-seven of 200 patients completed the study. Baseline visual analogue scores (0–10 scale) for pain were 6.40. There was a significant reduction in pain scores in the glyceryl trinitrate group (mean decrease 0.59, \( p < 0.05 \), 95\% confidence limits 0.04–1.14), 0.025\% capsaicin group (mean decrease 0.5, \( p < 0.05 \), 95\% confidence limits 0.05–1.05) and the glyceryl trinitrate capsaicin group (mean decrease 1.1, \( p < 0.05 \), 95\% confidence limits 0.22–1.98). Baseline discomfort of application scores were similar for all but the capsaicin groups (they were significantly higher (by 2.1 units, \( p < 0.001 \))). The odds ratio in favour of continuing treatment was 2.1 (95\% confidence limits 1.0–4.4) for glyceryl trinitrate and 2.4 (95\% confidence limits 1.2–5.1) for capsaicin and 5.0 (95\% confidence limits 3.8–6.4) for capsaicin GTN combination. The study showed that topical capsaicin and glyceryl trinitrate have an analgesic effect in painful osteoarthritis. When used together this effect is increased with the combination being more tolerable than capsaicin alone. Analgesic consumption is decreased by capsaicin, glyceryl trinitrate and to a greater extent by both combined. © 2000 European Federation of Chapters of the International Association for the Study of Pain

KEYWORDS: capsaicin, glyceryl trinitrate, osteoarthritis.

INTRODUCTION

The symptoms of osteoarthritis are common and the therapeutic options are limited by partial efficacy and side-effect profiles. The therapeutic aims are to palliate symptoms and to maximize quality of life and yet the therapeutic agents available to achieve this aim are limited by side-effects such as gastric bleeding with nonsteroidal anti-inflammatory agents (Blower et al., 1997) and analgesic tolerance with codeine based preparations.

The use of topical chilli pepper preparations as analgesics are not new with a report from 1850 of their use in the treatment of chilblains (Turnbull, 1850). It seems that it is the capsaicin fraction of the chilli pepper that has the analgesic effect and that effect is mediated by its
ability to reversibly deplete C-fibre afferent neurones of the neuropeptide Substance P (Rains and Bryson, 1995; Fitzgerald, 1983), which has an important role in the central transmission of noisceptive signals. An analgesic effect with topical application of capsaicin has been demonstrated in conditions as diverse as osteoarthritis (Deal et al., 1991; McCarthy et al., 1992; Altman et al., 1994), postmastectomy pain syndrome (Watson and Evans, 1992), painful diabetic neuropathy (Tandan et al., 1992; The Capsaicin Study Group, 1991) and postherpetic neuralgia (Watson et al., 1988; Watson et al., 1993; Bernstein et al., 1989). However, efficacy is compromised by the most prominent side-effect of topical application, burning discomfort at the application site, with 11 patients out of 33 dropping out in one study due to this discomfort (Watson et al., 1988).

Glyceryl trinitrate has a long pedigree in the treatment of angina pectoris and its topical form has been shown to have an analgesic effect in supraspinatus tendinitis (Berrazuela et al., 1996) and infusion related thrombophlebitis (Berrazuela et al., 1993). This effect may be mediated through its action on cyclic GMP (Feetisch and Neeck, 1987). We have previously demonstrated in a human volunteer study that addition of glyceryl trinitrate to capsaicin significantly reduces the burning discomfort after single application (McCleane and McLaughlin, 1998).

The aim of this study is to determine the analgesic effect and effect on tolerability of the addition of glyceryl trinitrate to capsaicin cream in patients with osteoarthritis.

METHOD

Subjects

A double blind, randomized, placebo controlled trial of 200 patients with pain due to radiologically proven osteoarthritis (hip, knee, shoulder or hand) presenting to a District General Hospital Pain Clinic. Previous treatment with nonsteroidal anti-inflammatory agents or simple analgesics (codeine or codeine / paracetamol combination) was either ineffective or complicated by intolerable side-effects. Those using nitrate preparations and those in whom concomitant medication was expected to change over the study period were excluded from the study. Patients were permitted to continue analgesics providing they continued the same preparation throughout the study period. Regional research ethics committee approval was granted for the study and all patients gave informed written consent. Pre-study calculation of sample size indicated that 68 patients per group would be required to demonstrate a 1 point fall in pain scores (90% power), while 17 patients would be required to show a 2 point fall (90% power). Patients were randomly allocated to one of four groups (A, B, C, D) in equal numbers using a computer generated random number list. These patients received (in a double blind fashion):

Group A – 0.025% capsaicin
Group B – placebo (capsaicin vehicle)
Group C – 1.33% Glyceryl trinitrate (two parts 2%glyceryl trinitrate, one part placebo)
Group D – 0.025% capsaicin, 1.33% glyceryl trinitrate (one part 0.075% capsaicin, two parts 2% glyceryl trinitrate)

All study creams were contained in a coded, but otherwise unlabelled dark glass container (these were prepared by Bioglan Laboratories Ltd). These creams were all off-white in colour, odourless and felt similar in texture immediately after application.

Patients were instructed to apply a volume of study cream equivalent to a grain of rice four times daily over a 6 week period to a single painful joint. They were further instructed not to wash that joint for at least 1 h after cream application and to avoid any eye contact.

Data

Patients were asked to record their average daily pain score for the previous 24 h at bed time each night using a 0–10 linear visual analogue score (0 = no pain, 10 = most amount of pain imaginable); to record their total daily analgesic consumption (number of tablets taken) again over the previous 24 h; and to record the discomfort of cream application using a 10 cm linear visual
analogue score (0 = no discomfort, 10 = most amount of discomfort imaginable). The number of patients wishing to continue using the study cream was also recorded. Only data from those completing the study period is included.

Statistical methods

Analysis of Variance (ANOVA) and Regression Techniques were used to examine the main effects of the study creams. Cusum analysis of daily means was used to provide information on where changes in patients' behavior tended to occur, and descriptive statistics of patients allocated to each treatment group. Patients' desire to continue with treatment was examined using logistic regression. Where results did not appear to be normally distributed, non-parametric tests were used in preference to parametric ones. Statistical analysis was assumed with p values < 0.05.

RESULTS

One hundred and sixty-seven patients provided results (83.5%). Of those who failed to provide results, 23 failed to attend review appointment, four used cream for less than 4 weeks and six used the cream provided but failed to record results. There were no statistically significant differences between the treatment groups in terms of sex distribution or age (Table 1(a)). The reference joint (hip, knee, shoulder or hand) was similarly distributed among the four groups (Table 1(b)).

Mean data for each variable was obtained and graphs of daily average pain scores, application discomfort scores and analgesic usage for each group was plotted. These graphs showed that there were no changes in these variables over the first 5 days of treatment, and so these values were taken as the baseline readings. One-way analysis of variance of baseline pain scores (mean scores of days 1 to 4) indicated no differences between treatment groups (F = 0.31 on 3 and 163 degrees of freedom; p > 0.05). There was a significant reduction in pain for patients using either glyceryl trinitrate (mean reduction 0.59, p < 0.05, 95% C.L. 0.04–1.14), capsaicin (mean reduction 0.5, p < 0.05, 95% C.L. 0.05–1.05) and the combination (mean reduction 1.1, p < 0.05, 95% C.L. 0.22–1.98) (Table 2). Pain scores in the placebo group increased by 0.24 (not significant) when compared to baseline levels. There was no significant difference between the fall in pain scores from baseline in the GTN and capsaicin groups; however, the difference between the fall in pain

### TABLE 1 (a). Patients characteristics.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Males</th>
<th>Females</th>
<th>Mean Age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>16 (40%)</td>
<td>24 (60%)</td>
<td>48.4 (14.11)</td>
</tr>
<tr>
<td>Glyceryl Trinitrate</td>
<td>22 (48%)</td>
<td>23 (51%)</td>
<td>48.1 (14.28)</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>23 (68%)</td>
<td>17 (42%)</td>
<td>49.7 (13.40)</td>
</tr>
<tr>
<td>GTN + Capsaicin</td>
<td>17 (41%)</td>
<td>25 (59%)</td>
<td>50.9 (12.75)</td>
</tr>
</tbody>
</table>

### TABLE 1 (b). Painful joint.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hip</th>
<th>Knee</th>
<th>Shoulder</th>
<th>Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
<td>15</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>GTN</td>
<td>11</td>
<td>19</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Capsaicin GTN</td>
<td>7</td>
<td>17</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

### TABLE 2. Mean pain scores (SD). 0–10 visual analogue score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.36</td>
<td>6.64</td>
<td>6.54</td>
<td>6.31</td>
<td>6.28</td>
<td>6.60</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>6.48</td>
<td>6.49</td>
<td>6.19</td>
<td>6.00</td>
<td>5.99</td>
<td>5.98</td>
</tr>
<tr>
<td>GTN</td>
<td>6.36</td>
<td>6.04</td>
<td>5.77</td>
<td>5.97</td>
<td>5.95</td>
<td>5.77</td>
</tr>
<tr>
<td>Capsaicin / GTN</td>
<td>6.81</td>
<td>6.44</td>
<td>6.11</td>
<td>6.00</td>
<td>5.87</td>
<td>5.71</td>
</tr>
</tbody>
</table>

* * p < 0.05

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scores between the capsaicin GTN combination and the other active treatments was statistically significant ($p < 0.05$).

The Kruskal–Wallis one-way analysis of variance of ranks indicated significant differences between treatment groups in terms of discomfort of application ($\chi^2 = 24.91$ on 3 degrees of freedom; $p < 0.001$). In particular, those allocated to the capsaicin group appeared to have worse baseline discomfort (Table 3). Only the baseline discomfort score was found to be statistically significant in regression analysis. Discomfort of application falls by about a third of their original values over the 6 week period, irrespective of the treatment. The addition of glyceryl trinitrate to capsaicin reduces baseline discomfort.

One-way analysis of variance of daily usage (tablets) of analgesics in week 1 indicated no differences between treatment groups ($F = 0.60$ on 3 and 163 degrees of freedom; $p > 0.05$) with a mean analgesic consumption of four tablets daily. There was a significant reduction in usage of analgesics for people treated with glyceryl trinitrate or capsaicin, the effect of their combined use being additive (Table 4).

Three out of 40 patients wished to continue placebo cream, 11/45 glyceryl trinitrate, 11/40 capsaicin and 15/45 glyceryl trinitrate capsaicin combination. These results were analysed by logistic regression with glyceryl trinitrate, capsaicin and the interaction between glyceryl trinitrate and capsaicin as explanatory variables. There was a significant increase in the odds ratio in favour of staying on treatment for both glyceryl trinitrate ($OR = 2.1; 95\%$ confidence limits $1.0–4.4$) and capsaicin ($OR = 2.4; 95\%$ confidence limits $1.2–5.1$) when compared to placebo. The odds ratio in favour of staying on the combined preparation was $5.0$ ($95\%$ C.L. $3.8–6.4$).

**DISCUSSION**

Our results indicate that analgesic benefit can be derived in patients with osteoarthritis who repeatedly apply either capsaicin or glyceryl trinitrate creams to a painful joint and that the combination of both together is more effective and more tolerable than either alone. The significant number of patients who elected to continue on their study medication in the combined group is a testimony to its efficacy and tolerability. The population studied was not a representative spectrum of adult patients with osteoarthritis pain but rather those in whom more conventional agents had either not been tolerated or had been ineffective. To have demonstrated both a statistical and clinical reduction in pain scores in this group indicates that either single constituent creams or the combination of both together may be a useful addition to our treatment options for patients with painful osteoarthritis. Patients are in particular attracted to the notion of applying medication to that area which is affected. Despite an apparent medical prejudice against topical preparations (Bateman and Kennedy, 1995; Anonymous, 1994), the experience with topical anti-inflammatory agents suggests that patients' preferences in this respect are generated not only by the apparent reduction in side-effects but also by real clinical efficacy (Moore et al., 1998). The place of these drugs in the treatment algorithm.

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**TABLE 3. Mean baseline application discomfort scores (SD). 0–10 visual analogue score.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean application discomfort (SD)</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.90 (2.24)</td>
<td>0.21–1.59</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>2.41 (2.87)**</td>
<td>1.52–3.30</td>
</tr>
<tr>
<td>GTN</td>
<td>1.03 (2.25)*</td>
<td>0.37–1.69</td>
</tr>
<tr>
<td>Capsaicin / GTN</td>
<td>1.69 (2.94)*</td>
<td>0.83–2.55</td>
</tr>
</tbody>
</table>

* $p < 0.05$; ** $p < 0.001$

**TABLE 4. Mean daily analgesic use (week six), (number of tablets taken per day). Pretreatment mean analgesic consumption was four tablets per day.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean daily analgesic use</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>GTN</td>
<td>3.52**</td>
<td>0.16</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>3.72*</td>
<td>0.16</td>
</tr>
<tr>
<td>Capsaicin / GTN</td>
<td>3.25**</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* $p < 0.05$; ** $p < 0.01$