For more information,
please contact
NUTRITION CARE ASIA PTE LTD
Thomas Khoo at +65 97452152

A double-blind, randomised, placebo controlled trial of the analgesic properties of curcumin (Nalgesic® Active Ingredient Cumerone 1200®) in osteoarthritis of the hand.

Greg Tooley[1,3], Luke Xantidis[1,3] & Daniel Lewis[2,3]

[1] School of Psychology, Deakin University

[2] Lewis Institute for Health & Wellbeing

[3] Integrative Health Research Unit, Faculty of Health, Medicine, Nursing and Behavioural Sciences, Deakin University

Integrative Health Research Unit

Deakin University

Conflict of interest declaration:

- This paper presents study which was run with in-kind support only from Nutrition Care Pharmaceuticals ***(NCP)***. This supported entailed the supply of active and placebo preparations in coded packages. While the researchers have previously conducted trials which were partly funded by NCP, this trial was conducted using departmental resources of the Integrative Health Research Unit, Deakin University. Nalgesic® Active Ingredient Cumerone 1200® is the product name distributed under the NCP banner, while Nalgesic® is the same product distributed under the Brighthope brand.

INTRODUCTION

Osteoarthritis (OA) is a complex group of conditions which are difficult to diagnose and define (Symmons, Mathers & Pfleger, 2003). OA has been described by the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee (Altman et al., 1986) as "A heterogenous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins" (p. 1039). OA has been estimated to cause symptoms and functional impairment that adversely affect quality of life to a greater degree than chronic respiratory, cardiovascular or gastrointestinal disorders (Longyhore & Seaton, 2003). According to a World Health Organisation Burden of Disease Project (Woolf & Pfleger, 2003), the condition is characterised clinically by joint pain, tenderness, limitation of movement, and variable degrees of local inflammation. Osteoarthritis may occur in any joint, however it is most usually diagnosed as occurring in the hip, knee, and joints of the hand, foot, or spine. Definition and diagnosis is complex because assessment may be undertaken through either X-ray examination of joint space narrowing, or clinical criteria including the presence of joint pain on most days.

In people over the age of 60 years worldwide, it is estimated that 9.6% of men and 18.0% of women have symptoms associated with OA (Murray & Lopez, 1996). The incidence of OA in the US has been estimated at 12% of population (Barclay, Tsourounis, & McCart, 1998). OA incidence is higher in women than men, with an approximate ratio of two to one. Although OA is responsible for significant morbidity from pain and loss of function, and is one of the most common forms of rheumatic disease, the precise biochemical cause of OA is unknown (Barclay et al., 1998; da Camara & Dowless, 1998). However, it is known that the process of the disease is characterised by a degradation of cartilage proteoglycans and of subchondral bone, which over time leads to a functional deterioration of the joint. This deterioration often results in the painful features of OA (da Camara & Dowless, 1998).

Consistent with world trends, Australian estimates have indicated that the incidence of OA is higher among women than men (2.95 per 1000 compared to 1.71 per 1000 for men) across all age groups. The highest incidence for women occurs in the 65-74 year age group, reaching approximately 13.5 per 1000 population per year. Among men the highest incidence occurs in the group over 75 years of age (approximately 9 per 1000 population per year) (Mathers, Vos, & Stevenson, 1999). Among those younger than 45 years men are affected more often than women, whereas over 55 years of age women are more frequently affected than men. Apart from increasing age, obesity is a risk factor in the development and progression of OA in men and women (REF).

Murray and Lopez (1996) estimated that OA was the eighth leading non-fatal burden of disease in the world in 1990, and that it accounted for 2.8% of total years of living with disability. This is approximately the same percentage as schizophrenia and congenital anomalies (Woolf & Pfleger, 2003). Woolf and Pfleger have noted that with extended life expectancies in future years the corresponding increase in age of populations will result in greater numbers of people with the condition.

OA of the hand

Treves et al. (1995) reported that, after the knees and hips, the fingers are the third most common site of OA. In a review of therapeutic trials in digital OA they found that, although the condition is commonly occurring, inconsistencies in definitions and methods of diagnosis mean that hand OA is controversial and is therefore rarely examined in clinical trials. When OA of the hand is studied, as in the American College of Rheumatology study designed to develop criteria for the classification and reporting of OA of the hand (Altman et al., 1990), OA is classified or diagnosed according to OA symptoms being present at multiple finger-joint sites. In their 1990 study of patients with OA, Altman et al. reported that pain was present in 37% of OA patients in the first carpometacarpal (CMC) joint (the base of the thumb).

Treatments for OA

Deal and Moskowitz (1999) reviewed a number of treatments that have been indicated as beneficial in the treatment of OA. They listed three major treatment modalities: Non-Pharmocologic Treatments (including Patient education, exercise, weight loss, and joint protection), Pharmacologic Therapy (including analgesics, intra-articular steroids, and nonsteroidal anti-inflammatory drugs or NSAIDs), and Surgical Approaches (including arthroscopic debridement, osteoectomy, and total joint arthroplasty). The use of these methods individually or in combination is dependent on various factors such as disease stage, severity of symptoms, patient tolerance etc. and it is not proposed here to review their relative efficacy.

The most commonly used treatment, nonsteroidal anti-inflammatory drugs or NSAIDs are associated with significant side effects most commonly gastric and cardiac. The recent removal from sale of a drug in this class Vioxx due to toxicity concerns, has highlighted the potential difficulties in using these drugs in long term chronic conditions.

Curcumin

Curcumin (diferuloylmethane) is a component of the spice turmeric which is used widely in eastern cooking but has also been used in India to treat various conditions such as rheumatism, bodyache, inflammations (Pari, Tewas and Eckel, 2008). More recently, it has been suggested that turmeric may be beneficial in the treatment of a number of health conditions due to its purported anti-oxidant (Betancor-Frenandez, Perez-Glaves, Siez and Stahl, 2003), anti-tumour (Jaggetia & Aggerwal, 2007), and anti-inflammatory effects (Jackson, Higo, Hunter and Burt, 2006).

Early studies into the anti-rheumatic activity of curcumin showed promising results. Deodhar et al. (1980) conducted a double-blind crossover study in 18 patients to compare anti-rheumatic effects of 1200mg/day curcumin and 300mg/d phenylbutazone (a non-steroidal anti-inflammatory drug). Patients showed significant improvement of symptoms (duration of morning stiffness, walking time and joint swelling) after administration of curcumin. This study indicated that curcumin was well tolerated, had no reported side-effects and showed comparable anti-rheumatic activity to the NSAID.

In the light of such promising results, Satoskar, Shah and Shenoy (1986) used curcumin to treat post-operative inflammation following inguinal hernia or hydrocoele surgery. Patients received either 400mg/tid curcumin, 100mg/tid phenylbutazone, or 250mg/tid lactose placebo for a total of five days. Satoskar et al (1986) reported that curcumin and phenylbutazone were both significantly more effective than placebo in producing an anti-inflammatory effect.

More recently Lal, Kapoor et al. (2000) and Holt, Katz and Kirshoff (2005) have conducted trials in which curcumin was used to successfully treat idiopathic inflammatory orbital pseudotumours and inflammatory bowel disease respectively. A study of 182 patients with rheumatoid arthritis and joint swelling showed a significant inter-group difference at the end of the 16 weeks of therapy. Participants in the trial were receiving 1200mg of curcumin daily (Chopra., et al., 2000) In another trial it was demonstrated that curcumin had an anti-inflammatory effect and assisted in the reduction of stiffness and joint swelling (Funk, Oyarzo, et al., 2006)

In addition, Lubbad, Oriowo and Khan (2009) have articulated and tested the molecular mechanism of this potential anti-inflammatory effect concluding that the anti-inflammatory effect of curcumin effect has legitimacy at a molecular level. Curcumin inhibits the expression of the cyclooxygenase isoform COX-2 at the transcriptional level (Menon and Sudheer, 2007). Cyclooxygenaseis a key mediating enzyme in prostaglandin synthesis from arachadonic acid which is associated with the inflammatory response (Sharafkhaneh, Velamuri, Badmaev, Lan and Hanania, 2007).

The development of Nalgesic® Active Ingredient Cumerone 1200®

It is perhaps impressive that the findings detailed above with respect to the analgesic properties of curcumin have been achieved despite the well-documented fact that the substance exhibits generally poor bioavailability. This is due generally to its poor absorption, and rapid metabolism and elimination (Aggarwal & Harikumar, 2009). As such, the utilisation of curcumin as a clinically effective, reliable analgesic in humans has been somewhat dependent on attempts to increase both the longevity of its presence in the circulation, and its cellular penetration. Various means, including the concomitant administration of piperine (Shoba et al., 1998), have been employed or are under investigation (Aggarwal & Harikumar, 2009).

It is in this context that Nalgesic® Active Ingredient Cumerone 1200® has been developed by NCP and its partners. Nalgesic is a proprietary formulation, where the curcumin has been blended to achieve superior absorption for greater effect and faster onset of action. As such, the manufacturers and distributors of Nalgesic® claim to have a product with enough penetration and perseverance to compete with widely available NSAIDs in terms of both the extent and length of the analgesic effects while being virtually free of any of the unwanted iatrogenic effects associated with that class.

We proposed to objectively test these claims by conducting a study to assess whether the symptoms of pain associated with inflammation in osteoarthritis of the thumb joint may be ameliorated by the use of Nalgesic® Active Ingredient Cumerone 1200®.

In the context of the discussion above, we undertook a double blinded, fully randomised, placebo controlled trial of curcumin (Nalgesic® Active Ingredient Cumerone 1200®) in 10 patients with OA of the carpal-metacarpal joint of the thumb. It was hypothesised that, compared to placebo, patients undergoing treatment with Nalgesic® Active Ingredient Cumerone 1200® would demonstrate significantly greater reductions in their subjective experiences of pain when performing tasks with their affected joint. In addition, when compared to the placebo condition, it was hypothesised that patients in the Nalgesic® Active Ingredient Cumerone 1200® treatment group would demonstrate enhanced performance of these tasks as measured by dolorimeter and an increased range of movement as measured by a goniometer. Finally, we will explore the nature of any dose-response property of Nalgesic® Active Ingredient Cumerone 1200® via comparison of outcome measures in a single (1200mg/d) dose and a ‘double’ (2400 mg/d) dose.

Method

Ten volunteers with a clinical diagnosis of OA of the carpal metacarpal joint of the thumb were randomly allocated to a treatment sequence which was in turn randomly assigned. Patients were recruited from the clinical practice of Dr Lewis, and all met the relevant criteria for the diagnosis of osteoarthritis of the carpal-metacarpal joint of the thumb.

Following recruitment and provision of informed consent, patients were allocated a treatment order according to a computer generated key that ensured both patient and experimenter remained unaware of treatment until the trial had concluded. Participants were asked to refrain from taking any of their preferred analgesics on the day of testing.

Each participant blindly underwent all three treatment conditions (placebo, Nalgesic® Cumerone 1200mg and Nalgesic® Cumerone 2400mg) as allocated, across three days, each of which was separated by a week. Participants typically arrived at the clinical laboratory between 9:00 and 9:30 a.m. Treatment (dose) was administered at 10:00 a.m., immediately following the baseline assessment. Placebo and Nalgesic® tablets were identical in appearance. Doses were pre-prepared so that the placebo condition the provision of two placebo tablets, the 1200mg condition entailed the provision of 1 placebo and 1 active (Nalgesic® Active Ingredient Cumerone 1200®) tablet and the 2400mg condition entailed the provision of 2 active (Nalgesic® Active Ingredient Cumerone 1200®) tablets. For each condition, each participant was required to undergo the same pre-post measurements of the outcome measures outlined below:

Grip strength measurement via digital dynamometer: grip strength was measured as kilograms of pressure for three different grip patterns, each of which depended on the involvement of the thumb: tip grip, key grip, and pen grip. These grips were chosen because they emulate the types of behaviours associated with activities of daily living which people with OA of the thumb typically have difficulties with.

Subjective (VAS) pain ratings related to grip: As well as measuring grip strength in each of the three positions, we measured associated pain on a 10-pont Visual Analogue Scale (VAS). Range of motion (Opposition and Extension of thumb was measured using a goniometer. Subjective (VAS) pain ratings related to range of movement (flexion and extension of thumb and forefinger). Subjective (VAS) pain ratings related to the movement of thumb opposition (Tip of thumb to the tip of the little finger and the palm at the base of the little finger.

Post-measures were retaken at 12:00p.m., 2:00 p.m. and 4:00 p.m. (respectively 2, 4 and 6 hours post-treatment). In the interim, participants remained sedentary, but were free to talk, read, watch movies etc. After the final measurements were taken on the third testing day, the experimenter was unblended and participants were informed of the treatment order and were invited to discuss their results with Dr Lewis. Patients were paid $100 per day for their participation.

Results

All patients completed each phase of the trial without any side effects of treatment being reported.

Analytic Procedure:

Data were analysed primarily via repeated measures ANOVA, where two planned contrasts were conducted for each outcome measure. The Single Dose (1200mg) group was first compared to the Placebo group to establish whether the typically recommended dose of Nalgesic® could demonstrate analgesic qualities over and above anything that could be attributed to the placebo effect. The second contrast compared the Single-Dose condition with the Double-Dose condition (2400mg) to establish if greater doses of Nalgesic® had demonstrably stronger analgesic effects. Significant interactions between time and treatment were investigated further using GLM Contrasts.

Grip Strength

Figure 1, below, summarises the finding that grip strength increased, by approximately 25% following treatment in both the Nalgesic®groups. A significant interaction between treatment and time was found on the grip strength measures $F_{(3,27)}$ =8.29, p<0.001 for the placebo vs single-dose comparison. There was no significant interaction between time and treatment $F_{(3,27)}$ =0.28, p>0.05 when comparing the single- and double-dose groups. For both Nalgesic groups, Grip strength improved significantly in the 2 hours following treatment (p<.005) and remained significantly higher than at baseline at 4 hours (p<.01) and 6 hours (p<.05).

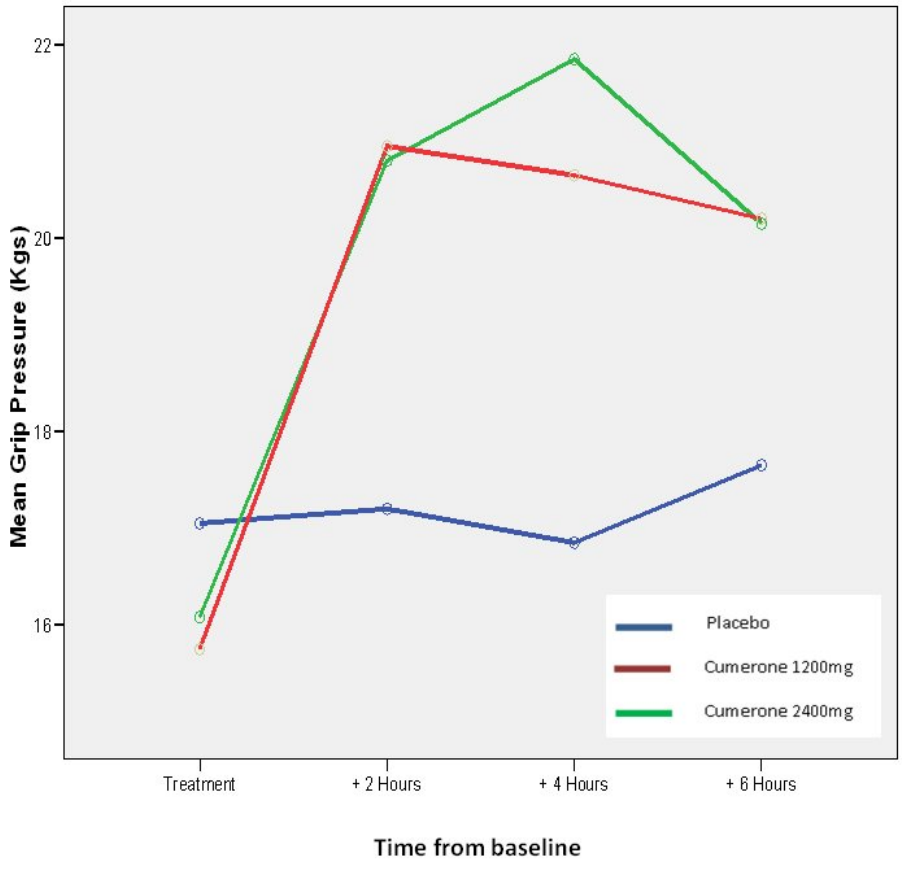

Figure 1. Mean grip strength measured over time for each of the three treatment conditions.

Pain Associated with Gripping

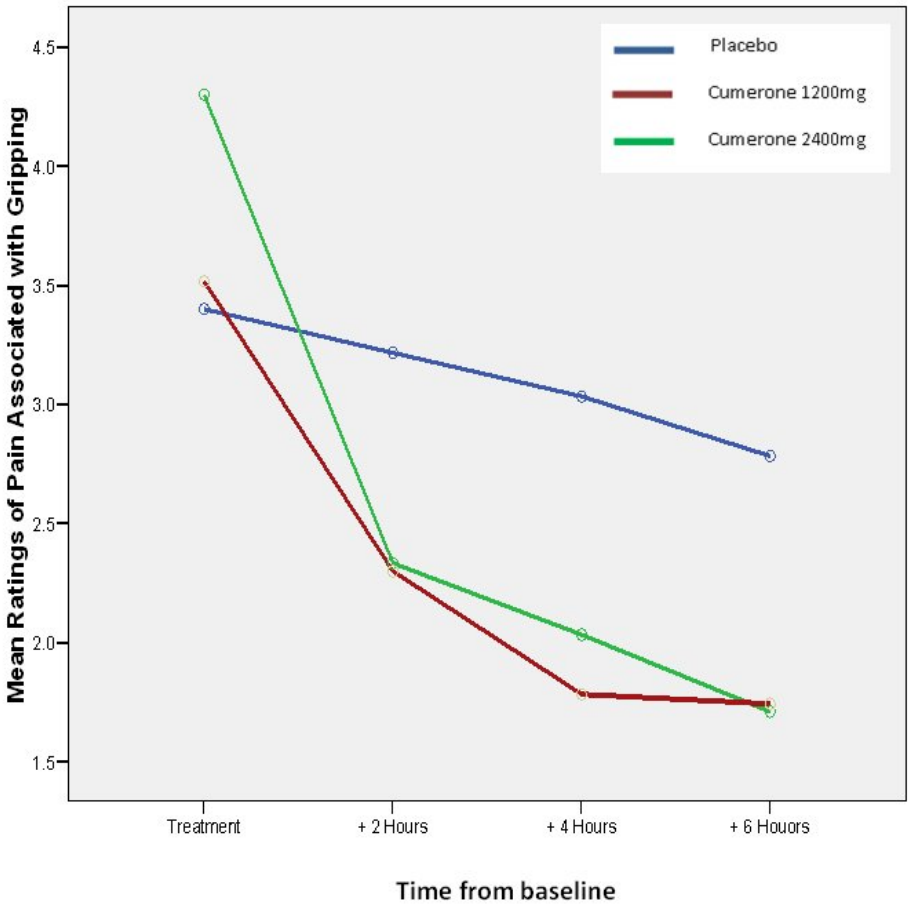

Figure 2. Mean ratings of pain associated with gripping measured over time for each of the three treatment conditions.

Figure 2, above, depicts the general finding that pain associated with gripping decreased in all groups following treatment, although the effects was again more substantial (greater than 50% reduction) in both Nalgesic® groups. Confirming this, a significant interaction between treatment and time was found on the grip strength measures $F_{(3,27)}$ =4.29, p<0.05 for the placebo vs single-dose comparison. There was no significant interaction between time and treatment $F_{(3,27)}$ =0.42, p>0.05 when comparing the single- and double-dose groups. The general trend for pain to subside across the period of the trial just attained overall significance (p<.05), however, no post-treatment point was significantly lower than at baseline cor the placebo group. For both Nalgesic® groups, pain associated with gripping decreased significantly in the 2 hours following treatment (p<.05) and remained significantly lower than at baseline at 4 hours and at 6 hours (p<.05).

Range of Movement

Figure 3, below shows similar trends to those found in the grip strength data, however, time by treatment interactions in the range of movement data failed to attain statistical significance in both the single-dose/placebo $F_{(3,27)}$ =2.12, p>0.05 and the single-dose/double-dose $F_{(3,27)}$ =0.78, p>0.05 comparisons.

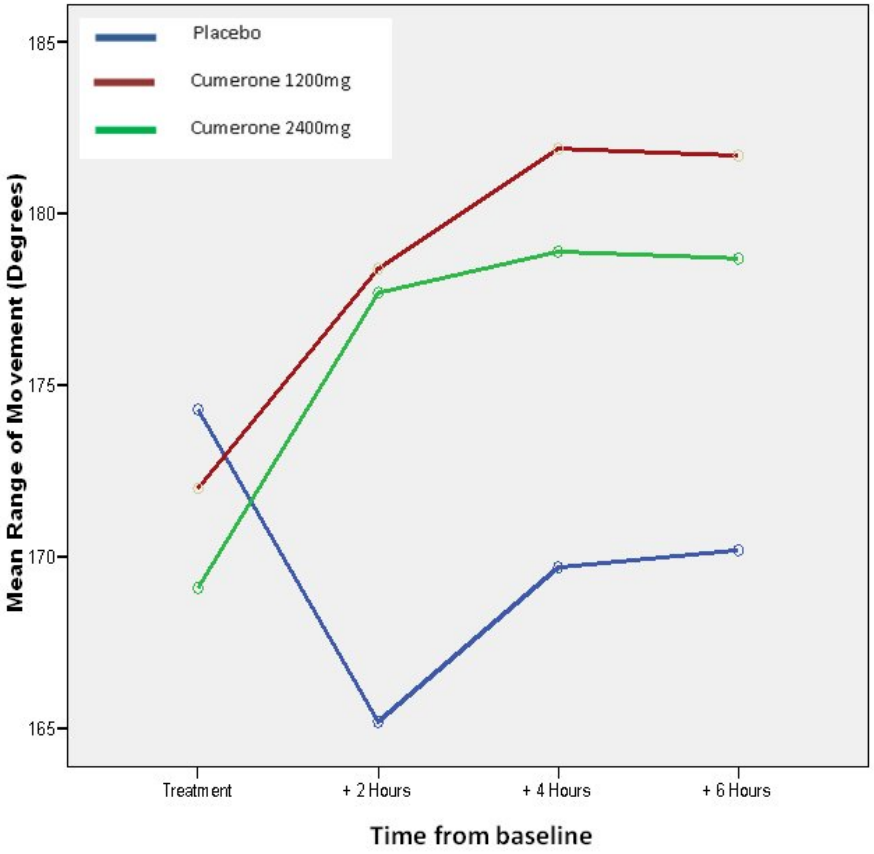

Figure 3. Range of movement of the thumb at each time point for each group

Pain associated with Extension and Opposition of the Joint

Figure 4, below shows that all groups experienced less pain on joint opposition as the study went on through the day $F_{(3,27)}$ =5.41, p<0.01, however, time by treatment interactions in the range of movement data failed to attain statistical significance in both the single-dose/placebo $F_{(3,27)}$ =1.33, p>0.05 and the single-dose/double-dose $F_{(3,27)}$ =0.17 p>0.05 comparisons. As such, although the reduction in pain associated with joint flexion appeared to be greater, it was not substantially different enough from the effect of the placebo to attain statistical significance.

Mirroring the results outlined above for pain associated with joint opposition, Figure 5, below shows that all groups experienced less pain on joint extension as the study went on through the day $F_{(3,27)}$ =4.11, p<0.05, however, time by treatment interactions in the range of movement data failed to attain statistical significance in both the single-dose/placebo $F_{(3,27)}$ =2.15, p>0.05 and the single-dose/double-dose $F_{(3,27)}$ =1.53 p>0.05 comparisons. As such, although the reduction in pain associated with joint extension appeared to be greater, it was not substantially different enough from the effect of the placebo to attain statistical significance.

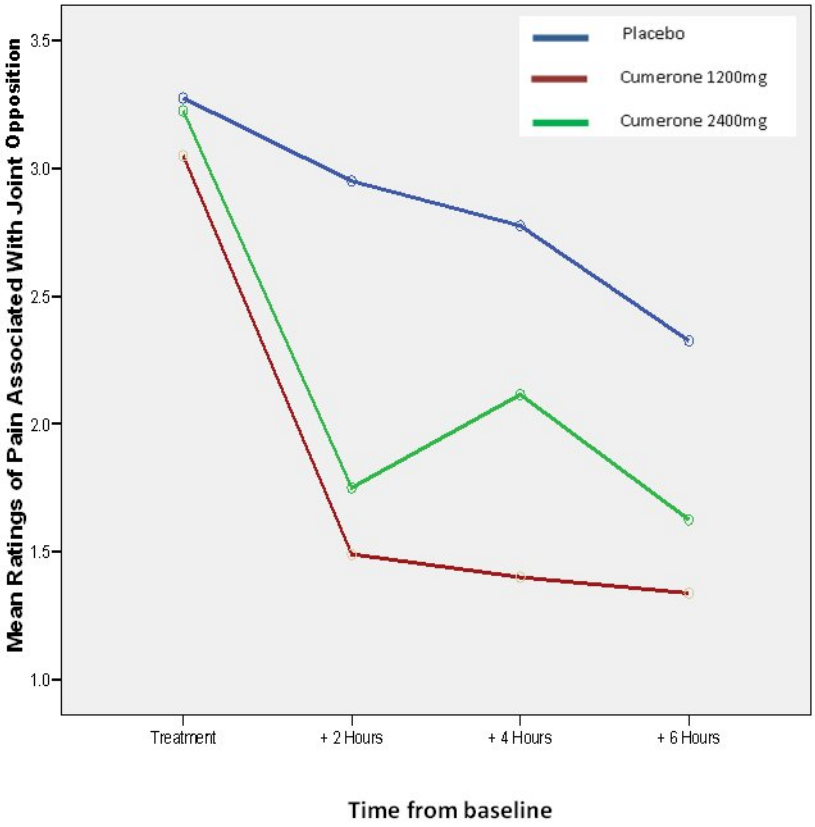

Figure 4. Pain associated with thumb opposition (curling the thumb-tip back to the palm and tip of the little finger) at each time point for each group.

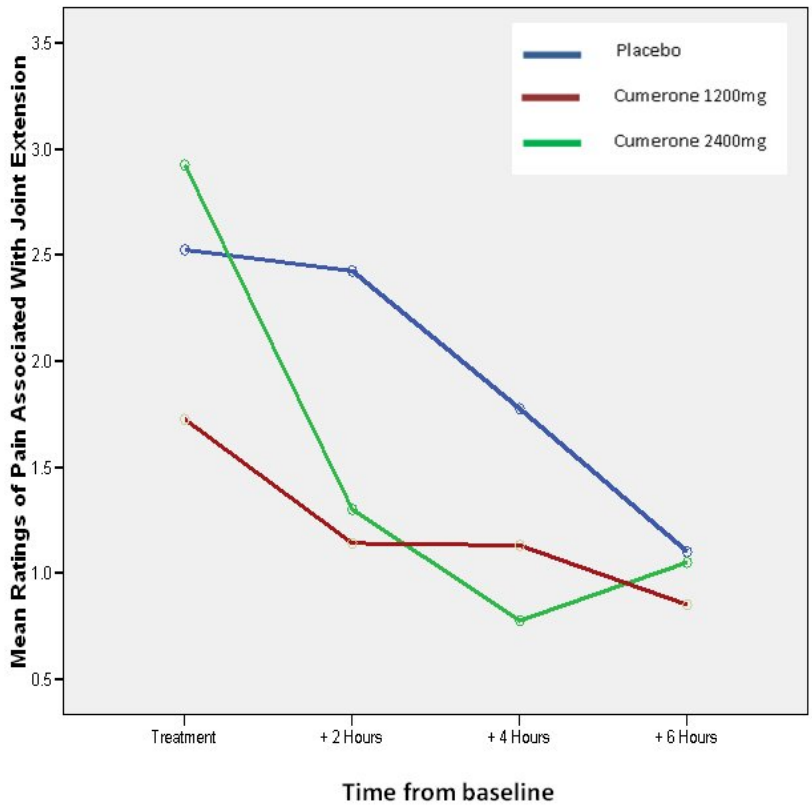

Figure 5. Pain associated with extension of the thumb (drawing the thumb tip as far away from the tip of the index finger as possible) at each time point for each group.

Discussion & Conclusions

Summary of Results

The groups treated with Nalgesic® active Ingredient Cumerone 1200® demonstrated clear increases in their grip strength in functionally relevant clinical tests (key, tip and pinch grip). These increases were significantly greater than anything that could be attributed to placebo responding or other factors, such as circadian influences on pain sensitivity. It is worth noting that these results probably understate the analgesic effect of Nalgesic® active Ingredient Cumerone 1200®, given that, across the group, pain decreased significantly despite the fact that gripping strength actually increased. The effect was apparent for the entire 6 hours of the study.

Similar trends were apparent for changes in range of movement and associated pain, however these trends failed to attain statistical significance, probably because range of movement was not substantially inhibited, compared to grip strength, in this group of patients.

Discussion

The findings regarding increases in grip strength and concurrent reduction in pain are impressive. Another striking feature of the data is that, even where differences between placebo and active treatment conditions were not statistically significant, patients in the Nalgesic® active Ingredient Cumerone 1200® treated conditions repeatedly demonstrated a steep fall in pain (or increase in grip strength and range of movement) within the first two hours, while changes in the placebo group are always more gradual and occur across the six hour period. This is consistent with the claim that Nalgesic® active Ingredient Cumerone 1200® has active analgesic effects which have reasonably rapid onset (ie less than 2 hours) and persist for several hours following administration.

The gradual changes observed in the placebo group are, of course, consistent with there being a placebo effect, but are likely to be driven, in part by normal circadian mediated reductions in pain and stiffness that occur from morning to afternoon in osteoarthritis of the hand, and many other similar conditions (Bellamy, Sothern, Campbell & Buchanan, 2002). Circadian changes alone, however, certainly could not explain the rapid changes experienced in the active treatment groups, although it is possible that they contributed in a minor fashion to the longevity of the effects demonstrated here.

Finally, it is noteworthy that the double dose of Nalgesic® active Ingredient Cumerone 1200® did not have more significant effects than the single dose condition. The ten patients involved in the trial were, however, generally of moderate to small stature, and higher doses may be required in larger patients in order to achieve the same analgesic effects demonstrated in this group.

Further research is required to establish the generalisability of Nalgesic's analgesic effects in different conditions and at different times of day.

Conclusions

This trial was doubly-blinded, and placebo controlled. Patients were randomly allocated to treatment orders and all patients completed the entire trial. In this context, the findings are considered to be reliable, despite the relatively small sample size.

Following administration of Nalgesic® active Ingredient Cumerone 1200®, patients in this trial demonstrated clear increases in grip strength (approx 25%), they also reported less pain (approx 50%) associated with gripping. The measures employed closely correspond to the circumstances in which patients with OA of the thumb experience pain and subsequent impairment in daily activities (e.g. using keys, turning taps, picking up and/or using various utensils etc...). As such, the analgesic effects of Nalgesic® active Ingredient Cumerone 1200® are likely to be clinically and functionally relevant to patients, especially those who do not tolerate other analgesics and/or anti-inflammatory medications well.

The findings offer strong support to the claims that Nalgesic® active Ingredient Cumerone 1200® has analgesic properties (at least) which are both statistically and clinically significant. Larger doses may be required by patients who are of larger stature. Further research is required to determine Nalgesic® active Ingredient Cumerone 1200®) therapeutic impact at other times of day, in other conditions, and relative to other treatments for pain and inflammation.

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