"Celecoxib improves the efficiency of the locomotor mechanism in patients with knee osteoarthritis. A randomised, placebo, double-blind and cross-over trial."

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ABSTRACT

OBJECTIVE: To compare the effect of celecoxib vs placebo treatment on clinical and gait variables in knee osteoarthritis (OA) patients; focusing on the efficiency of the locomotor mechanism. METHODS: STUDY DESIGN: A prospective, randomised, double-blind placebo-controlled trial. PATIENTS: Eight adult patients with painful OA of the knee. OUTCOME MEASURES: Clinical assessment included knee pain assessed by the visual analogue scale, range of knee motion assessed by goniometer, and locomotor function status assessed by a Knee Score Scale. Gait was assessed by means of instrumented analysis including synchronous kinematic, dynamic, electromyographic, and energetic recordings. STATISTICAL ANALYSIS: The effect of treatment on the primary variable, the efficiency of the locomotor mechanism, and on secondary clinical and gait variables was assessed by the Hills and Armitage non-parametric approach. RESULTS: Celecoxib treatment improved the efficiency of the locomotor mechanism significantly. Among the secondary outcome measures assessed, celecoxib treatment improved walking cadence and reduced the knee pain significantly. CONCLUSION: This study shows that celecoxib is effective in improving locomotor function and pain in patients with knee OA.

CITE THIS VERSION

Celecoxib improves the efficiency of the locomotor mechanism in patients with knee osteoarthritis. A randomised, placebo, double-blind and cross-over trial

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Summary

Objective: To compare the effect of celecoxib vs placebo treatment on clinical and gait variables in knee osteoarthritis (OA) patients; focusing on the efficiency of the locomotor mechanism.

Methods:
Study design: A prospective, randomised, double-blind placebo-controlled trial.
Patients: Eight adult patients with painful OA of the knee.
Outcome measures: Clinical assessment included knee pain assessed by the visual analogue scale, range of knee motion assessed by goniometer, and locomotor function status assessed by a Knee Score Scale. Gait was assessed by means of instrumented analysis including synchronous kinematic, dynamic, electromyographic, and energetic recordings.
Statistical analysis: The effect of treatment on the primary variable, the efficiency of the locomotor mechanism, and on secondary clinical and gait variables was assessed by the Hills and Armitage non-parametric approach.

Results: Celecoxib treatment improved the efficiency of the locomotor mechanism significantly. Among the secondary outcome measures assessed, celecoxib treatment improved walking cadence and reduced the knee pain significantly.

Conclusion: This study shows that celecoxib is effective in improving locomotor function and pain in patients with knee OA.

Key words: Locomotor mechanism, Celecoxib, Knee osteoarthritis, Gait.

Introduction

Osteoarthritis (OA) is the most common joint disorder, accounting for significant disability and health care expenditure. Nonsteroidal anti-inflammatory drugs (NSAID) have long been used to treat pain and joint inflammation and to improve gait. Celecoxib and rofecoxib were subsequently introduced as highly selective inhibitors of cyclooxygenase-2 (COX-2) which improved pain and inflammation with less gastrointestinal side effects. The efficacy of celecoxib and rofecoxib on pain, stiffness, and joint inflammation has been established. The gait of patients with knee OA is affected by pain and stiffness, but quantifiable outcome measures are necessary if one is to compare the benefits of different treatments. Only limited data are currently available on the effects of NSAIDs on gait variables and there is none on COX-2 inhibitors in patients with knee OA. We hypothesised that knee stiffness and pain can affect the kinematics of the lower limbs. It is possible to study the effects of these abnormalities on the efficiency of the locomotor mechanism using measurement of mechanical work and energy. These mechanical and metabolic measurements may be relevant to disability in ambulatory patients and may also be useful in clinical research to improve knowledge of the effects of treatment. By studying the energy changes of the centre of body mass (CMb) it is also possible to gain further insight into the mechanisms responsible for abnormal gaits and whether or not the normal walking mechanism is preserved in OA patients.

The aim of our study was to compare the effect of celecoxib vs placebo treatment on clinical, kinematic, electromyographic (EMG), mechanical and energetic gait variables in knee OA patients in a randomised, double blind, cross-over vs placebo trial, focusing specifically on the effects of treatment on the efficiency of the locomotor mechanism.

Patients and methods

PATIENTS

Eight adult patients (five women and three men, mean age of 65.5 ± 9 years, mean weight of 74.9 ± 14 kg, mean height of 1.65 ± 0.1 m; Table I) with painful and disabling OA of the knee were recruited consecutively from a rheumatology department by a single rheumatologist. All patients had radiological evidence of OA in the knee (grade II to IV on the Kellgren-Lawrence scale). All patients had difficulty in walking on flat ground but were able to walk without aids. Exclusion criteria were similar to...
those in previous studies. These included concurrent medical/arthritic diseases which could interfere with the assessments, such as secondary inflammatory arthritis, gout, isolated patellofemoral disease, a history of acute ligamentous or meniscal injury within the previous 2 years, or arthroscopy in the 3 months prior to study entry. Oral or intramuscular injection of corticosteroids within 4 weeks before study entry was also an exclusion criterion. Patients with hypersensitivity to one of the ingredients of celecoxib or rescue medication, patients with cardiological, respiratory or neurological disease, with gross obesity (Body Mass Index > 40), or with mental deficit were not included in the study. Patients with severe renal or hepatic insufficiency were also excluded, as were patients with acute or suspected gastrointestinal bleeding, or active gastric or duodenal ulcer.

**STUDY DESIGN**

This prospective, randomised, double blind, placebo-controlled study was conducted over an 8-month period in accordance with the principle of Good Clinical Practice guidelines of the regional drug control administration (Pfizer, Belgium). All patients gave informed consent and were recruited on a volunteer basis. The local ethics committee approved this study.

Seven days before the first clinical assessment (day 0, visit 1), the patients stopped their previous NSAID therapy to allow a full washout period based on the half-life of the molecule. On visit 2 (day 7) and visit 3 (day 21), clinical and gait assessments were performed, i.e., at the start of, and 14 days after, celecoxib 200 mg or placebo treatment. The patients then stopped treatment for a further 7 days to allow another washout period. They then started the second phase of the study taking the treatment they had not received during the first phase, i.e., placebo or celecoxib, for 14 days. On visit 4 (day 42), the fourth clinical examination and the third gait assessment were performed. Each assessment was made in the same conditions by the same examiner. The experimental design is summarised in Table II.

**TREATMENT**

Patients were randomly assigned to one of two groups (COX-2 or placebo). A single dose of celecoxib 200 mg or placebo provided by Pfizer, Belgium, was ingested with the evening meal once a day for 14 days. Paracetamol (6 × 500 mg/day max) was the only pain relief allowed if needed, and if taken was stopped 12 h before each assessment.

**OUTCOME MEASURES**

**Clinical assessment**

A safety evaluation was undertaken for each patient at each visit (1 to 4), noting the incidence and type of side effects. Clinical assessment included an estimate of knee pain on a 100 mm visual analogue scale (VAS). The range of knee motion was measured by a manual goniometer and locomotor function status assessed by the Knee Score Scale.

**Gait assessment**

Gait was assessed at visits 2, 3, and 4 by 3D instrumented analysis including synchronous kinematic, dynamic, EMG, and energetic recordings. Patients were instructed to walk at their self-selected speed. Foot-switch sensors were attached under the sole of the patients’ feet and recorded at 1000 Hz (Elite V5, Italy). These data were necessary to compute the global temporal parameters, i.e., walking speed, stride length, and cadence. Segmental kinematics were measured with the Elite system (Elite V5, Italy) and recorded at 50 Hz. Four CCD infrared cameras measured the coordinates, in the three spatial planes, of 19 markers.
reflective markers positioned on specific anatomical landmarks to compute angular displacements of joint segments. Each patient recorded 10 ± 2 trials. All trials were normalised to 100%; 0% corresponding to the initial foot contact of the OA leg. On the OA lower limb, several angular parameters of the knee (Kv-flexion at heel strike; Kf-maximum flexion at loading response; Kp-maximum flexion in swing phase) were assessed.

The ground reaction forces (GRF) were simultaneously recorded by a 1.8 m long, 0.6 m wide strain-gauge force platform (Pharos System, USA) at 50 Hz mounted at ground level in the middle of the walkway (10 m). The external mechanical work, Wext, i.e., the work performed by the muscles to lift and accelerate the CMb relative to the surroundings during walking, was computed from the GRF following the method described in detail by Cavagna. The 3D accelerations of the CMb were computed from the vertical, lateral, and forward raw components of the GRF and the mass of the patient. The mathematical integration of the 3D accelerations gave the 3D speeds of the CMb, allowing computation of the CMb kinetic energy due to forward (Ekf), vertical (Ekv), and lateral (Ekl) speeds. A second mathematical integration of vertical CMb speed gave the vertical displacement (Sv) of the CMb. From the vertical displacement (Sv) of the CMb, the instantaneous gravitational potential energy (Ep) was computed. The total external mechanical energy of the CMb was computed as the sum of gravitational potential energy and kinetic energies. The increments of external kinetic energy, Ek, Ekv, Ekf, and Ep represented the positive work necessary to accelerate the CMb in the three directions and to lift the CMb (Wext, Wext, Wext, Wext), and calculated during a stride. Wext during gait was defined by summing the increments of the total mechanical energy curve during a stride. Wext, Wext, Wext, Wext, and Wext are expressed per unit distance and per kg body mass. The Recovery, quantifying the amount of energy-saving transfer between gravitational potential energy and kinetic energy of the CMb, i.e., an index reflecting the efficiency of the pendulum-like mechanism of walking, was calculated as:

\[ \text{Recovery} = 100 \times \frac{W_{\text{ext}} + W_{\text{ext}} + W_{\text{ext}} + W_{\text{ext}} - W_{\text{ext}} - W_{\text{ext}}}{W_{\text{ext}} + W_{\text{ext}} + W_{\text{ext}} + W_{\text{ext}} + W_{\text{ext}}} \]

where \( |W_{\text{ext}}| + |W_{\text{ext}}| + |W_{\text{ext}}| + |W_{\text{ext}}| \) represents the maximum work one should do without energy shift, and the work actually done, \( W_{\text{ext}} \). A 100% recovery would require the kinetic and potential curves to be exactly opposite in phase and of equal shape and amplitude according to a purely ballistic movement. In this case, the frequency of ballistic movement (f_b) is calculated as:

\[ f_b = 2\pi \sqrt{\frac{l}{g}} \]

where \( l \) is the leg length of the subject, i.e., the distance between the greater trochanter and the ground and \( g \) the gravitational acceleration.

The electrical activity of the Rectus Femoris (RF) and Biceps Femoris (BF) muscles was recorded by a telemetric EMG system (BTS, Italy) with surface electrodes. The signal was digitised at 1000 Hz, full-wave rectified and filtered (bandwidth 25–300 Hz). The onset and cessation of muscle activity were visually determined. The EMG activity of each muscle was normalised in 100% of stride time. The co-contraction time index between RF and BF muscles was temporally quantified as the percentage of the stride during which antagonistic muscles were simultaneously activated.

Force, kinematics, EMG and foot-switch signals were recorded simultaneously and synchronised by two photocells. The information from photocells, placed at the level of the neck of the patient to avoid interference with movements of the upper limbs, was used to calculate the mean forward speed by dividing the distance between the photocells, i.e., 1.8 m or the length of platform, by the time taken to cross them.

Directly after the level ground evaluation, the assessment of metabolic energy cost was performed on a motor driven treadmill (Mercury LT med, Germany). Breath by breath rates of oxygen consumption and carbon dioxide production were measured with an ergospirometer (Quark b2, Italy). Values were automatically converted by a software program (Cosmed Quark B2 win, v 5.1.a) to standard temperature, pressure, and dry oxygen consumption. The measurement of the rate of oxygen consumption involved a rest period with the patient standing on the treadmill, followed by a walking period at a gait speed equivalent to the average gait speed adopted during assessment on level ground. The patients were asked to walk for at least 2 min after they reached steady state. The respiratory quotient (RQ), determined by the ratio between the rate of carbon dioxide production and the rate of oxygen consumption, was always less than one. Joules of energy expended per litre of oxygen consumed were computed, depending on the RQ. The net energy rate was the energy expended during gait minus the energy expended at rest expressed in J kg⁻¹ min⁻¹. The net rate of energy expenditure was then divided by the gait speed of the patient to obtain the net energy cost of gait (C) expressed in J kg⁻¹ m⁻¹.

### Statistical Analysis

Our data were computed by an independent, blinded statistician (Data Investigation Company Europe, Belgium). The effects of treatment (celecoxib vs placebo treatment) on the primary variable, i.e., the effect on the efficiency of the locomotor mechanism was assessed using the Hills and Armitage non-parametric approach as specified in the trial protocol. Secondary outcomes including the effects of treatment on clinical and gait variables were also assessed by the Hills and Armitage non-parametric approach. The Hills and Armitage non-parametric approach involves initial calculation, for each patient, at what has been referred to as a basic estimator. This is the difference between the two treatments (A or COX-2 vs B or placebo treatment) or treatment effect for a given patient. This procedure ignores the baseline but can be considered safe as there is no problem of carry-over.

### Results

The statistical analysis of results is presented in Table III. The results showed that a treatment effect was present. The primary variable defined in our initial protocol was significantly improved by celecoxib treatment. In fact the efficiency of the locomotor mechanism expressed by the recovery index (see Fig. 1(C)) was significantly improved (P = 0.03) by celecoxib treatment (44 ± 5% at placebo and 53 ± 4% at celecoxib visits). The recovery index increased because of a significantly better phase time course (P = 0.03) between potential and kinetic energy changes. At placebo visit, the CMb potential energy reached its
maximum value $8.1 \pm 6$ ms before the CMb kinetic energy reached its minimum. After celecoxib treatment, the CMb potential energy reached its maximum value $1.7 \pm 1$ ms before the CMb kinetic energy reached its minimum. This time course reflects an improved locomotor mechanism.

Two secondary outcome measures were also improved by celecoxib treatment. The mean VAS score of knee pain [see also Fig. 1(A)] was significantly ($P = 0.03$) decreased between placebo ($34 \pm 31$) and celecoxib ($22.5 \pm 15$) visits. The mean cadence [see Fig. 1(B)] was significantly ($P = 0.03$) increased between placebo ($88 \pm 5$ step min$^{-1}$) and celecoxib ($95 \pm 5$ step min$^{-1}$) visits. However, the other secondary outcome variables were not improved by the treatment. The mean range of knee motion ($121 \pm 14^\circ$ in COX-2 group vs $122 \pm 14^\circ$ in placebo group) and the median knee function score ($90$ [range $45$–$100$] in COX-2 group vs $95$ [range $45$–$100$] in placebo group) were not affected by treatment. The mean spontaneous walking speed ($2.6 \pm 0.6$ km h$^{-1}$ in COX-2 group vs $2.5 \pm 0.4$ km h$^{-1}$ in placebo group) and the step length ($0.48 \pm 0.1$ m in COX-2 group vs $0.48 \pm 0.07$ m in placebo group) were unchanged. The mean knee angular displacement at initial contact ($K_1: 6 \pm 6^\circ$ in COX-2 group vs $6 \pm 9^\circ$ in placebo group), at maximum flexion in loading response ($K_2: 12 \pm 7^\circ$ in COX-2 group vs $10 \pm 10^\circ$ in placebo group), and at maximum flexion in swing phase ($K_3: 49 \pm 6^\circ$ in COX-2 group vs $48 \pm 13^\circ$ in placebo group) were not affected by treatment. The mechanical work ($W_{ext}$: $0.35 \pm 0.07$ J kg$^{-1}$ m$^{-1}$ in COX-2 group vs $0.43 \pm 0.1$ J kg$^{-1}$ m$^{-1}$ in placebo group) and the cost ($C$: $3.35 \pm 2$ J kg$^{-1}$ m$^{-1}$ in COX-2 group vs $3.71 \pm 2.7$ J kg$^{-1}$ m$^{-1}$ in placebo group) were not significantly improved after celecoxib treatment. The time of co-contraction was not affected by treatment ($40 \pm 10\%$ in COX-2 group vs $36 \pm 8\%$ in placebo group).

Discussion

The clinical efficacy of celecoxib in reducing knee pain in patients with OA has been demonstrated in previous studies$^{1,6}$. However the efficacy of celecoxib on measurable parameters of gait has not yet been established$^{4,5}$. The results of this study show mainly that celecoxib treatment improved the efficiency of the locomotor mechanism.

During walking, CMb displacement can be compared to the displacement of an inverted pendulum. At each stride, the CMb is successively behind, or in front of the point of contact with the foot on the ground. When the CMb is behind the point of contact, the link to the ground causes a forward deceleration (therefore a decrease in kinetic energy) and a vertical rise in the CMb (therefore an increase in gravitational potential energy). Some of the kinetic energy due to the forward speed is converted into gravitational potential energy. As the CMb moves past the point of contact on the ground, the link to the ground allows a decrease in the height of the CMb and a concomitant increase in the

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Table III

<table>
<thead>
<tr>
<th>Primary variable</th>
<th>Treatment effect ($P$ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficiency of the locomotor mechanism (Recovery)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Secondary variables

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Treatment effect ($P$ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS knee pain</td>
<td>0.030</td>
</tr>
<tr>
<td>Range of knee motion</td>
<td>0.657</td>
</tr>
<tr>
<td>Function Knee Score</td>
<td>1.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gait assessment</th>
<th>Treatment effect ($P$ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed</td>
<td>0.112</td>
</tr>
<tr>
<td>Step length</td>
<td>1.00</td>
</tr>
<tr>
<td>Cadence</td>
<td>0.030</td>
</tr>
<tr>
<td>$K_1$</td>
<td>0.885</td>
</tr>
<tr>
<td>$K_2$</td>
<td>0.471</td>
</tr>
<tr>
<td>$K_3$</td>
<td>0.471</td>
</tr>
<tr>
<td>$W_{ext}$</td>
<td>0.112</td>
</tr>
<tr>
<td>$C$</td>
<td>0.471</td>
</tr>
<tr>
<td>Index of co-contraction</td>
<td>0.112</td>
</tr>
<tr>
<td>Time phase $E_f - E_i$</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Significant differences are typed in bold.
forward speed, as some of the gravitational potential energy is converted back into kinetic energy like a pendulum. However, humans are not ideal frictionless pendulums, so the kinetic and potential energy is not perfectly conserved. The recovery is a measure of the amount of muscular work undertaken during the pendulum exchange between potential and kinetic energy, and attains a maximum of 65% during normal gait at optimal speed\textsuperscript{14}. The recovery is a good reflection of the efficacy of the locomotor mechanism in a pathological gait\textsuperscript{15}. In this study, we have shown that recovery was significantly improved by celecoxib treatment with a concomitant decrease in pain as indicated by a significant decrease of VAS knee pain score. As knee pain decreased, the stride cadence increased with an increase in leg stiffness. The increase in stride cadence increases whole-body vertical stiffness\textsuperscript{16} and is accompanied by a tendency to shift from a compliant towards a rigid mechanism of walking. The marked increase in cadence suggests that the contractile component of muscles progressively plays a less important role, when compared with their elastic component. An increase in cadence requires a stiffer spring (more contracting fibres in the leg muscles)\textsuperscript{17}, the elastic component. An increase in cadence enables one to get nearer the line connecting the centre of mass with the ground. Thisline connecting the body mass centre and the body structures connecting the body mass centre and the line connecting the centre of mass with the ground. This stiffer spring generates a shift towards a rigid mechanism of walking revealed by an increase in the percentage of recovery. The increase in cadence enables one to get nearer the optimal step frequency \((f_0)\) calculated according to a purely ballistic movement, without muscular contraction. Thus the increase in cadence improves the efficiency of the locomotor mechanism following treatment with celecoxib.

**Conclusion**

This study has shown that celecoxib improves the efficiency of the locomotor mechanism and confirmed previous studies\textsuperscript{1,4} that have demonstrated clinical efficacy for reduction of knee pain in patients with OA.

**References**


**Annexe: glossary abbreviation**

BF: Biceps Femoris muscle.
C: net oxygen cost.
CM\(_b\): the centre of the body of mass.
\(E_{ki}\): kinetic energy of the CM\(_b\) due to its velocity in the forward direction.
\(E_{kl}\): kinetic energy of the CM\(_b\) due to its velocity in the lateral direction.
\(E_{kv}\): kinetic energy of the CM\(_b\) due to its velocity in the vertical direction.
\(E_{p}\): gravitational potential energy of the CM\(_b\).
\(GRF\): ground reaction forces.
Hz: Hertz.
\(K_f\): knee flexion at heel strike.
\(K_{fl}\): maximum knee flexion at loading response.
\(K_s\): maximum knee flexion at swing phase.
Recovery: percentage of energy recovered over a stride by an interchange between potential and kinetic energy.
RF: Rectus Femoris muscle.
RQ: respiratory quotient: ratio between the rate of carbon dioxide production and the rate of oxygen consumption.
\(S_v\): vertical CM\(_b\) displacement.
\(W_{alm}\): work to accelerate the CM\(_b\) in forward direction.
\(W_{all}\): work to accelerate the CM\(_b\) in lateral direction.
\(W_{av}\): work to accelerate the CM\(_b\) in vertical direction.
\(W_{p}\): positive work to lift the CM\(_b\).
\(W_{ext}\): positive mechanical work performed by muscles to lift and accelerate the CM\(_b\).