Original Article

# Efficacy and safety of short-term use of COX-2 inhibitors in patients after an acute stroke with musculoskeletal pain

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## Abstract

**Objective:** Musculoskeletal pain commonly occurs in the elderly, many of whom are also prone to suffer from strokes. We studied whether short-term use (≤ 4 weeks) of cyclooxygenase-2 (COX-2) inhibitors for musculoskeletal pain in stroke patients helped them to participate in their therapies and was safe and efficacious. **Materials and Methods:** Three hundred and three patients admitted consecutively with first ischemic stroke were studied. Two cohorts were defined, based on whether patients with acute stroke had sufficient musculoskeletal pain that warranted oral COX-2 inhibitors (COX-2 group) or not (case-matched controls). Primary efficacy measures were change in Fugl-Meyer (F-M) pain score and change in total functional independence measure (TFIM) scores on discharge from hospital. Safety was judged by the incidence of vascular episodes during the study period. **Results:** From the original 303 patients, 64 patients in the COX-2 group were matched with 64 patients in the non-COX-2 group. The groups were matched for age (±5 years), gender, and admission TFIM score (± 5 points). Baseline characteristics between the 2 groups were similar. The primary and secondary outcome measures were similar between the 2 groups, except for ambulation endurance, which favored the non-COX-2 group ($P < 0.03$). Greater change in the pain score (less pain) was found in the COX-2 group; this effect was strongest in patients who were independent prior to their stroke (on post hoc analysis). There were too few adverse events in either group of any significance. **Conclusions:** The short-term use of COX-2 inhibitors reduced musculoskeletal pain in acute stroke patients, improved functional motor outcome, and were found to be safe.

## Key Words

COX-2 inhibitors, functional independence measure, rehabilitation, stroke

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## Introduction

More than 25% of stroke patients experience musculoskeletal pain that limits their participation in therapy and hinders their functional rehabilitation recovery.[1,2] Musculoskeletal pain in stroke patients is caused by an inflammatory response, mediated by prostanoids, serotonin, bradykinin, and histamine. COX-2 inhibitors are frequently prescribed to patients with musculoskeletal pain because they are as effective as nonsteroidal anti-inflammatory drugs (NSAIDs) in relieving arthritic pain, and have less gastrotoxicity.[3,4]

Recently, there has been heightened concern regarding the COX-2 inhibitor's cardiovascular safety. The anti-inflammatory effects of COX-2 inhibitors, particularly decreased prostacyclin ($PGI_2$), causes increased platelet aggregability and vasoconstriction (promoting a prothrombotic state), and this action is thought to increase the frequency of angina pectoris, myocardial infarction, and stroke recurrence.[5] Although the Celecoxib Long-term Arthritis Safety Study (CLASS) showed no significant difference in the frequency of cardiovascular events when compared with NSAIDs,[6] the Vioxx (rofecoxib) Gastrointestinal Outcome Research Study (VIGOR) showed Vioxx to have a relative risk of 2.38 for developing a confirmed thrombotic cardiovascular event compared with naproxen.[7] This conflicting result was due to the type of patient population studied, the duration for which the medication was administered and, more importantly, Vioxx is 9 times more potent an inhibitor of the COX-2 enzyme than celecoxib. Solomon *et al*.[8] found rofecoxib use was associated with an elevated relative risk of acute myocardial infarction (AMI) compared with celecoxib. Use of celecoxib was not associated with an increased relative risk of AMI in this study. The more recent Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) showed that the incidence of cardiovascular events did not differ between lumiracoxib and either ibuprofen or naproxen, irrespective of aspirin use.[9,10] The Adenoma Prevention with Celecoxib Study (APC), studied prevention of colorectal adenomas,[11] and the Adenomatous Polyp Prevention on Vioxx (APPROVe)

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determined the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas.[12] Both studies showed significantly increased cardiovascular risks. These last two studies (APC and APPROVe) were ultimately responsible for inducing the pharmaceutical manufacturers to take their medications off the market.[12]

Recent studies in patients recovering from stroke have demonstrated that several frequently used drugs, such as benzodiazepines, haloperidol, dilantin, and opiates, have been found to impede functional motor recovery.[13] Therefore, we decide to test the hypothesis prospectively that short-term (≤ 4 weeks) use of COX-2 inhibitors would improve their rehabilitation functional recovery by decreasing their musculoskeletal pain and increasing their participation in their rehabilitation therapies. Second, the safety of COX-2 medications was examined, particularly with regard to frequency of cardiovascular events, such as angina pectoris, myocardial infarction, and recurrent stroke during this inpatient study period in this high-risk patient population.

## Materials and Methods

### Patients

All stroke patients consecutively admitted to a designated stroke rehabilitation unit during a 12-month period were studied. Stroke diagnosis was based on clinical history, neurologic examination, and confirmatory head computed tomography/magnetic resonance imaging studies. The inclusion criterion for this study was first ischemic stroke, because this is an ideal patient population in which to study the potential increase in "atherothrombotic risk" associated with long-term use of NSAIDs. The exclusion criterion was hemorrhagic stroke or a history of recurrent ischemic strokes. Stroke patients with significant musculoskeletal pain that interfered with poststroke rehabilitation programs received COX-2 inhibitors (celecoxib or rofecoxib) only. These patients continued with their prescribed antiplatelet medications for secondary stroke prophylaxis, including aspirin. None of these patients took NSAIDs while on COX-2 inhibitors. Local Institutional Review Board approval was obtained for this study.

The admitting physician assessed the patient's neurologic impairments on admission to the stroke rehabilitation unit. Stroke severity was graded using an ordinal neurologic impairment scale ranging from 1 to 3 (1 = motor impairment only; 2 = motor plus hemianopic vision or motor plus sensory impairment; 3 = motor plus hemianopic vision plus sensory impairment).[14] Motor weakness was evaluated using the Motricity Index (MI), a weighted score derived from Medical Research Council grades. Three movements are evaluated in both the upper limbs (pinch grip, elbow flexion, and shoulder abduction) and in the lower limbs (ankle dorsiflexion, knee extension, and hip flexion) with the patient lying in bed.[15] Homonymous visual field deficits (either hemianopsia or visual neglect) were assessed at the bedside by confrontation testing. Sensory impairment and proprioceptive loss were evaluated using the Limb Placement Task[16]; a mean error of >6 in. in the most affected quadrant indicates a significant somatic sensory deficit. Patients unable to comprehend this task after repeated gestural clues were scored as abnormal.[14] Cognitive functioning was evaluated using the Folstein Mini Mental State Examination (MMSE).[17] Depression, which is known to influence stroke functional outcome, was measured using DSM-IV criteria.

Of the 303 total patients who presented with first ever stroke during the 12-month study period, there were 64 patients with significant musculoskeletal pain (based on a score of ≥ 5 on a 0-10 numeric pain intensity scale) who were prescribed COX-2 inhibitors (Celebrex or Vioxx) for the length of their inpatient rehabilitation period (usually 4 weeks). These patients were matched with 64 patients who had no or mild musculoskeletal pain that did not warrant a COX-2 inhibitor, designated as the non-COX-2 group. The groups were matched for age, gender, and stroke severity; as these characteristics have been shown to influence rehabilitation outcomes.

**Table 1: Demographics of the 64 case–control pairs (Mean±SD)**

| Variable | Cox 2 given *n*=64 | No Cox 2 *n*=64 | *P* |
|---|---|---|---|
| Age, years (matched ±5) | 72.2±9.7 | 72.2±10.4 | 0.97 |
| Gender, M/F (matched) | 28/36 | 28/36 | na |
| Onset to admission, days | 21.0±35.7 | 16.6±23.5 | 0.43 |
| Adm. FM pain score (ns 62 and 53) | 75±16 | 76±18 | 0.36 |
| Dis. FM pain score (ns 56 and 55) | 77±16 | 75±19 | 0.55 |
| Lesion type | | | 0.72 |
| Embolic | 20 (31.3%) | 20 (31.3%) | |
| Thrombotic | 42 (65.6%) | 42 (65.6%) | |
| Carotid occlusion | 1 (1.6%) | 2 (3.1%) | |
| Ill-defined stroke | 1 (1.6%) | 0 (0.0%) | |
| Lesion site | | | 0.31 |
| Cortical left | 21 (33.1%) | 26 (40.5%) | |
| Cortical right | 32 (50.3%) | 21 (32.7%) | |
| Bilateral | 4 (6.6%) | 8 (12.5%) | |
| Brainstem/cerebellar | 4 (6.6%) | 7 (10.8%) | |
| Supra and infratentorial | 2 (3.4%) | 2 (3.4%) | |
| Independence | | | 0.29 |
| Without device | 52 (81.3%) | 58 (90.6%) | |
| With device | 9 (14.1%) | 5 (7.8%) | |
| Dependent | 3 (4.7%) | 1 (1.6%) | |
| Depression (ns 47 and 42) | 19 (40.4%) | 14 (33.3%) | 0.49 |
| MMSE(ns 33 and 28) | 21.0±7.1 | 17.4±10.6 | 0.11 |
| Stroke severity 1/2/3 | 32/16/16 | 36/22/6 | 0.057 |
| Deleterious medications 1/2 | 54/10 | 53/11 | 0.81 |
| Adm. FIM score (matched ±5) | 60±18 | 61±17 | 0.53 |
| Dis. FIM score | 79±20 | 79±18 | 0.84 |
| Adm. Mobility FIM score | 10.5±5.4 | 11.4±5.6 | 0.094 |
| Dis. Mobility FIM score | 18.2±7.0 | 19.7±6.2 | 0.076 |
| Adm. ambulation (ns 51 and 49) | 31±57 | 37±44 | 0.52 |
| Dis. ambulation (ns 57 and 59) | 118±204 | 149±230 | 0.27 |
| Adm. endurance (ns 64 and 63) | 67±87 | 79±73 | 0.27 |
| Dis. endurance (ns 64 and 63) | 294±274 | 418±388 | 0.028 |

F-M, Fugl-Meyer; FIM functional independence measure; MMSE, Mini-Mental State Examination; Adm., admission; Dis., discharge

**Table 2: Functional outcome measures (mean±SD) between the COX-2 and non-COX-2 group**

| Variable | Cox 2 given *n*=64 | No Cox 2 *n*=64 | *p* |
|---|---|---|---|
| Change in FIM score | | | |
| Total | 18±12 | 18±10 | 0.92 |
| ADL | 7.4±5.7 | 7.6±6.5 | 0.88 |
| Motor | 7.7±5.5 | 8.3±4.6 | 0.44 |
| Cognition | 2.5±3.4 | 2.2±3.0 | 0.57 |
| Change in ambulation | | | |
| Speed(ns 51 and 49) | 94±189 | 129±216 | 0.15 |
| Endurance (ns 64 and 63) | 227±263 | 340±342 | 0.03 |
| LOS(ns 63 and 59) | 27±10 | 25±11 | 0.44 |
| FIM efficiency (ns 63 and 59) | 0.30±0.56 | 0.36±0.55 | 0.52 |
| Change in the F-M pain score (ns 56 and 51) | 2.3±9.0 | 1.0±5.6 | 0.18 |

ADL, activities of daily living; F-M, Fugl-Meyer; FIM functional independence measure; LOS, length of stay; MMSE, Mini-Mental State Examination. ns 51 and 49 implies sample size for the 2 groups were 51 and 49 for that variable rather than 64 each

**Table 3: Frequency of adverse events for the two study groups**

| | COX-2 group (*n*=64) | Non-COX-2 group (*n*=64) |
|---|---|---|
| Upper gastrointestinal bleed | 1 | – |
| Abdominal pain | 1 | 1 |
| Myocardial infarction–acute | 2 | - |
| Renal failure | - | 1 |
| Stroke extension | - | 1 |

### Outcome measures

The Fugl-Meyer Assessment (FMA) scale is a well-designed, efficient clinical examination method widely used by therapists for evaluation of stroke patients. It is divided into 5 domains: Motor impairment, sensory impairment, balance, range of joint motion, and joint pain. Each domain has multiple items scored on a 3-point ordinal scale: 0 = cannot perform, 1 = performs partially, 2 = performs fully.[18] Both the motor and all other subsections of the FMA scale, have high inter- and intrarater reliability[19] and validity.[20] The FMA was administered by a trained therapist. The FMA pain scale, in which higher score means less pain assessed the patient's pain score on admission (total 88 points with 24 points for each upper extremity and 20 points for each lower extremity).

The study's functional outcome measures were changes in TFIM score and in FIM subscores for activities of daily living (ADL), motor, and cognition from rehabilitation hospital admission to discharge, length of stay (LOS) in days, FIM efficiency (defined as FIM change/LOS), and change in ambulation speed, and endurance. The TFIM was used to document the degree of disability a patient experiences, and the progress they make through programs of medical rehabilitation.[21] The TFIM is an 18-item ordinal scale scored from 1 to 7. A FIM item score of 7 is categorized as "complete independence," while a score of one is "total assist" in which a patient performs < 25% of a task. The FIM measures independent performances in self-care, sphincter control, transfers, locomotion, communication, and social cognition.[22] By adding the points for each item, the possible total score ranges from 18 (lowest functioning) to 126 (highest functioning). The FIM scale has been found to be a reliable[23] and valid measure.[24]

The ambulation velocity was measured using the 2-min, and ambulation endurance using the 6-min timed walking tests as described in "Guidelines for Pulmonary Rehabilitation Programs,"[25] both on admission and discharge. The 2- and the 6-min timed walking tests were administered by a physical therapist on admission. The patient was instructed to cover as much ground as possible in 6 min at a comfortable walking speed. Stop and rest periods were allowed during the evaluation. Patients ambulated with an orthotic device (ankle–foot or knee–ankle–foot orthosis), a walker (hemi or rolling), or a cane, if gait quality and/or safety were enhanced by such use. When patients needed assistance to ambulate during the timed walking test, the physical therapist could help advance the patient's weaker leg or provide assistance in weight-shifting. The physical therapist measured the distance covered using Trumeter Mini-Measure Distance-Measuring Wheel, a device that accurately measures up to 10,000 feet. The distances covered in feet, at both a 2-min and then at an additional 4-min time interval (for a total of 6 min) were noted separately. The ambulation speed was based solely on the 2-min portion of the total 6-min timed walking test, as it is not practical to carry out 2 separate timed walking tests on 2 separate occasions for every patient at admission. Both the 2- and 6-min timed walking tests are valid, reliable, and sensitive measures. Kosak *et al*. (2000) found the 2-min timed walking test to be the best measure for speed, and 12-min timed walk test to be the best measure for endurance.[26]

### Data analysis

Sixty-four stroke patients in the COX-2 group were matched with 64 stroke patients in the non-COX-2 group for age (±5 years), gender, and admission TFIM score (±5 points). A subset was selected in which both members of the pair were independent in their ADLs and mobility prior to their respective strokes (47 pairs). The subset was analyzed similarly to the analysis of the 64 pairs [Appendix 1 Tables]. In addition, the whole sample of 303 individuals (72 COX-2, 231 non-COX-2 group) was analyzed similarly to the 64 pairs [Appendix 2 Tables].

For all measures, descriptive statistics and results were expressed as either mean ± SD for continuous variables or as frequencies (percentages) for discrete variables. Differences between the COX-2 and non-COX-2 control groups at baseline were assessed using general linear model analyses for continuous variables and contingency table analyses for discrete

**Table A1.1: Demographics of the study population of 303 individuals (mean±SD)**

| Variable | Cox 2 given *n*=72 | No Cox 2 *n*=231 | *P* |
|---|---|---|---|
| Age, years | 71.9±10.5 | 68.1±13.6 | 0.03 |
| Sex M/F | 29/43 | 109/122 | 0.3 |
| Onset to admission, days | 20.4±34.1 | 16.7±22.0 | 0.9 |
| Adm. F-M pain score (ns 61 and 172) | 79±11 | 85±6 | 0.001 |
| Lesion type | | | 0.9 |
| Embolic | 22 (30.5%) | 69 (29.8%) | |
| Thrombotic | 48 (66.6%) | 156 (67.5%) | |
| Carotid occlusion | 1 (1.4%) | 5 (2.1%) | |
| Ill-defined stroke | 1 (1.4%) | 1 (0.4%) | |
| Lesion site | | | |
| Cortical left | 23 (31.9%) | 96 (41.5%) | |
| Cortical right | 35 (48.6%) | 78 (33.7%) | |
| Bilateral | 4 (5.5%) | 25 (10.8%) | |
| Brainstem/cerebellar | 7 (9.7%) | 24 (10.3%) | |
| Supra and infratentorial | 2 (2.7%) | 7 (3.0%) | |
| Independence | | | <0.001 |
| Without device | 58 (80.5%) | 207 (89.6%) | |
| With device | 11 (15.2%) | 17 (7.3%) | |
| Dependent | 3 (4.1%) | 7 (3.0%) | |
| MMSE (*n*=38 and 116) | 20.7±8 | 17.5±10.9 | 0.3 |
| Stroke severity 1/2/3 | 36/20/16 | 144/65/22 | 0.02 |
| Deleterious medications | 62/10 | 192/39 | 0.5 |
| Adm. FIM score (ns 71 and 217) | 60±18 | 67±19 | 0.01 |
| Adm. ambulation (ns 58 and 190) | 32±55 | 47±53 | 0.001 |
| Adm. endurance (ns 72 and 212) | 66±85 | 113±146 | <0.001 |

ADL, activities of daily living; F-M, Fugl-Meyer; FIM functional independence measure; LOS, length of stay; MMSE, Mini-Mental State Examination; Adm., admission; Dis., discharge

**Table A1.2: Functional outcome measures (mean±SD) between the COX -2 and non-COX-2 group**

| Variable | Cox 2 given *n*=72 | No Cox 2 *n*=231 | *P* |
|---|---|---|---|
| Change in FIM score | | | |
| Total (ns 71 and 223) | 18±12 | 18±11 | 0.9 |
| ADL (ns 72 and 215) | 7.6±6.3 | 7.8±6.3 | 0.9 |
| Motor (ns 72 and 215) | 7.2±5.2 | 8.2±4.5 | 0.3 |
| Cognition (ns 71 and 215) | 2.7±3.4 | 2.2±3.5 | 0.3 |
| Change in ambulation | | | |
| Speed (ns 58 and 189) | 103±201 | 161±231 | 0.001 |
| Endurance (ns 72 and 210) | 232±273 | 361±337 | 0.003 |
| LOS (ns 70 and 211) | 27±10 | 22±27 | 0.001 |
| FIM efficiency (ns 69 and 205) | 0.29±0.55 | 0.44±0.81 | 0.2 |
| Change in the F-M pain score (ns 54 and 156) | 2.1±7 | 0.5±5 | 0.1 |

ADL, activities of daily living; F-M, Fugl-Meyer; FIM functional independence measure; LOS, length of stay

variables. Changes in measurements from admission until discharge from the hospital were analyzed using general linear models. All statistical tests were two-tailed with significance threshold was set at 0.05. SPSS for Windows was used for the statistical calculations (release 17.0.0, SPSS Inc., 2008). Sample size for testing hypotheses relating to adverse events was estimated using PASS 2008 software (version 08.0.13, NCSS LLC, Kaysville, UT, USA, www.ncss.com, 2008).

## Results

There were no significant differences in the demographic variables between the 2 study groups (Cox-2 and non-Cox-2) as per [Table 1]. However, the non-Cox-2 group had a somewhat shorter onset-to-admission (17 vs 21 days), were marginally more independent prior to their stroke (91% vs 81%), and had slightly less severe strokes (6 vs 16) compared with the Cox-2 group.

The primary and secondary outcome measures were similar between the 2 groups ($P > 0.05$), except for the endurance measure, which favored the non-COX-2 group ($P < 0.03$) [Table 2]. This is not surprising given that pain is a limiting factor in the distance covered in a given time period. There was a decrease in pain in the COX-2 group as evidenced by the change in their F-M pain score

**Table A1.3: Frequency of adverse events for the two study groups**

| | COX-2 group (*n*=72) | Non-COX-2 group (*n*=231) |
|---|---|---|
| High-grade fever | – | 1 |
| Venous graft site infection | – | 1 |
| Upper gastrointestinal bleed | | 1 |
| Abdominal pain | 1 | 2 |
| Respiratory failure | | 1 |
| Chest pain –Pulmonary Embolism | – | 1 |
| Myocardial infarction–acute | – | 2 |
| Fast A fibrillation (new onset) | | 1 |
| Hypotensive episodes | | 1 |
| | 2 | |
| Renal failure | – | 1 |
| Hematuria | | 1 |
| | – | |
| Stroke–progression | | 3 |
| Seizure | | 2 |
| | 1 | |
| Hypoglycemic episode | – | 1 |
| | – | |
| | – | |
| | – | |

compared with the change in the pain score for the non-COX-2 group (2.3 ± 9 vs 1 ± 5.6, $P = 0.18$); however, this difference was not statistical. Similar differences were noted in the change in F-M pain score for the paired 47 stroke patients who were independent prior to their stroke in the COX-2 group ($n = 40$, 2.9 ± 9.3) compared with non-COX-2 group ($n = 38$, 1.1 ± 6.0) $P = 0.09$.

Adverse events (AEs) in the 2 study groups that required transfer back to an acute-care hospital were abdominal pain, upper gastrointestinal bleeding, AMI, stroke progression, and renal insufficiency [Table 3]. The AEs were comparable for the 2 study groups; the AEs rate for the COX-2 group (4 patients) was 0.06 with a 95% CI of 0.003–0.121, while for the non-COX-2 group (3 patients) was 0.04, with a 95% CI 0–0.098. Because too few AEs encountered in this study, and since the 95% CI overlapped between the 2 groups, the difference was not statistical.

## Discussion

This prospective, acute rehabilitation hospital-based study is the first of its kind to address the short-term use of COX-2 inhibitors in stroke patients with musculoskeletal pain undergoing inpatient rehabilitation. This study suggests COX-2 inhibitors help decrease pain and improve mobility with no detrimental effects on other functional outcome measures. This is an important outcome given that musculoskeletal pain due to osteoarthritis has been shown to impair stroke recovery.[27] There were no statistical differences in number of AEs between the COX-2 and non-COX-2 groups in this study.

Use of COX-2 inhibitors had negligible adverse effect on functional outcome variables measured by change in TFIM and FIM-ADL, FIM-mobility, and FIM-cognition subscores compared with the non-COX-2 group. In fact, the discharge FIM-mobility subscore

**Table A2.1: Demographics of the 47 case–control pairs with "independence" prior to admission (mean±SD)**

| Variable | Cox 2 given *n*=47 | No Cox 2 *n*=47 | *P* |
|---|---|---|---|
| Age, years (matched ±5) | 72.5±9.0 | 71.8±9.5 | 0.11 |
| Sex M/F (matched) | 18/29 | 18/29 | na |
| Onset to admission, days | 24.1±40.9 | 17.5±26.8 | 0.37 |
| Adm. F-M pain score (ns 45 and 39) | 74±17 | 76±19 | 0.33 |
| Dis. F-M pain score (ns 40 and 41) | 78±17 | 74±20 | 0.43 |
| Lesion type | | | 0.78 |
| Embolic | 15 (31.9%) | 13 (27.7%) | |
| Thrombotic | 31 (66.0%) | 32 (68.1%) | |
| Carotid occlusion | 1 (2.1%) | 2 (4.3%) | |
| Lesion site | | | 0.12[c] |
| Cortical left | 16 (34.0%) | 21 (44.7%) | |
| Cortical right | 24 (51.1%) | 12 (25.5%) | |
| Bilateral | 3 (6.4%) | 7 (14.9%) | |
| Brainstem/cerebellar | 3 (6.4%) | 6 (12.8%) | |
| Supra and infratentorial | 1 (2.1%) | 1 (2.1%) | |
| Independence | | | na |
| Without device | 47 (100%) | 47 (100%) | |
| With device | | | |
| Dependent | | | |
| MMSE (ns 20 and 19) | 19.8±7.8 | 15.4±10.6 | 0.15 |
| Stroke severity 1/2/3 | 25/10/12 | 29/14/4 | 0.084 |
| Deleterious medications 1/2 | 41/6 | 39/8 | 0.56 |
| Adm. FIM score (matched ±5) | 60±19 | 60±18 | 0.39 |
| Dis. FIM score | 76±20 | 79±18 | 0.24 |
| Adm. Mobility FIM score | 10.2±5.7 | 11.5±5.8 | 0.16 |
| Dis. Mobility FIM score | 17.4±6.8 | 19.6±6.3 | 0.028 |
| Adm. ambulation (ns 38 and 37) | 29±64 | 38±46 | 0.75 |
| Dis. ambulation (ns 41 and 43) | 89±183 | 134±203 | 0.21 |
| Adm. endurance (ns 47 and 46) | 58±77 | 80±69 | 0.057 |
| Dis. endurance (ns 47 and 46) | 282±283 | 428±393 | 0.030 |

F-M, Fugl-Meyer; FIM functional independence measure; MMSE, Mini-Mental State Examination; Adm., admission; Dis., discharge

showed a trend favoring the COX-2 group ($P = 0.076$). Because the primary and secondary outcome measures were similar between the 2 groups, a post hoc analysis was undertaken, where 47 pairs of patients who were independent prior to their stroke was used. This analysis showed the discharge FIM-motor subscore was significantly higher for the COX-2 group (17.4 ± 6.8 vs 19.6 ± 6.3, $P = 0.028$), and there was also a trend in the change in the F-M pain score favoring patients in the COX-2 group ($P = 0.09$). Thus COX-2 inhibitors facilitate improvement in the functional motor outcome measures of stroke patients with pain. This improvement does not appear to be due to a decrease in the ischemia-induced brain injury secondary to neutralization of COX-2 dependent inflammatory cytokines, because upregulation of COX-2 mRNA usually begins 4–6 h after ischemia, reaching a maximum at 12–24 h and usually lasting until 98 h, in animal models.[28] Other authors have shown significant musculoskeletal pain reduction in humans assigned to the COX-2 inhibitor group within a week of starting the medication and persisting for the length of the study.[29]

There were few AE rates noted in this study overall. AEs that required transfer back to acute-care hospitals, in both groups,

included AMI, acute gastrointestinal bleeding, abdominal pain, renal impairment, and stroke progression. This study did not show any significant differences in AE numbers or severity between the 2 study groups. The reasons for a low AE rate (especially for cardiovascular events) could be due to the short time period (≤4 weeks) for which the COX-2 inhibitors were prescribed, and use of antiplatelet agents or anticoagulant for ischemic stroke prophylaxis.[30] A future prospective, randomized COX-2 inhibitor study during the initial poststroke period of 96 h should be undertaken to study the medications effect on neurologic impairment and functional outcome measures using sample size based on this study power analysis. Based on the observed numbers of AEs, a sample of 547 matched pairs (1094 individuals: 547 COX-2, 547 non-COX-2) would be required to show a statistically significant difference in cardiovascular events in the COX-2 group compared with the non-COX-2.

## Conclusions

This study showed that short-term use of COX-2 inhibitors in stroke patients admitted to an acute rehabilitation unit, with musculoskeletal pain, improved functional outcome measures and did not increase the vascular risk for adverse events compared with those stroke patients without pain who were not on COX-2 inhibitors.

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