Etoricoxib improves osteoarthritis pain relief, joint function, and quality of life in the extreme elderly

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ABSTRACT

Etoricoxib is a selective cyclooxygenase-2 inhibitor, with a lower risk of gastrointestinal toxicity compared to traditional nonsteroidal anti-inflammatory drugs (NSAIDs). We evaluated the effectiveness and tolerability of etoricoxib in extremely elderly patients with chronic pain due to osteoarthritis (OA). A prospective, single-center, single-arm study was conducted, enrolling 19 extremely elderly men with OA (mean age 85.9, range 79-96 years), who responded inadequately to NSAIDs or other analgesics. Patients were switched to etoricoxib, 60 mg once daily for 4 weeks, without prior medication washout. Data were recorded before and after etoricoxib treatment. The primary endpoint was improvement in pain, assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) after the 4-week treatment. Other endpoints included the Brief Pain Inventory Short Form (BPI-SF), Treatment Satisfaction Questionnaire for Medication (TSQM), Short Form 36 (SF36), and European Quality of Life-5 Dimensions (EQ-5D). Safety and tolerability were assessed by collecting adverse events data. Pain and disability scores measured by WOMAC index were lower after treatment (pain, $p \leq 0.001$; disability, $p = 0.020$). BPI-SF showed a significant improvement in joint function when walking and performing normal work (walking, $p = 0.021$; normal work, $p = 0.030$). SF36 scores improved for 7 out of 11 items after etoricoxib treatment (#1, $p = 0.032$; #4, $p = 0.026$; #5, $p = 0.017$; #6, $p = 0.008$; #7, $p = 0.009$; #8, $p = 0.013$; and #10, $p = 0.038$). EQ-5D showed a significant improvement in visual analogue scale scores ($p = 0.036$). TSQM results demonstrated a higher patient perception of overall satisfaction. No adverse events were reported. Pain relief, joint function, quality of life, and treatment satisfaction improved significantly in elderly patients with OA after etoricoxib administration.

KEY WORDS: Pain; extreme elderly; osteoarthritis; etoricoxib; joint function; quality of life
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INTRODUCTION

Chronic pain negatively affects sleep in elderly patients and restricts their daily activities [1,2]. Other common consequences of persistent pain include depression, anxiety, decreased socialization, and impaired ambulation [1,3]. Substantial pain is often undertreated, especially in older adults and nursing home residents [1,3]. Much of this pain is a result of rheumatic disorders, predominantly osteoarthritis (OA) [4,5].

OA is the most common form of arthritis in the elderly [6]. In its severe form, the chronic pain can significantly reduce the overall quality of life [6-10]. Current projections indicate that OA may become the fourth leading cause of disability worldwide by the year 2020 [6,11], underscoring the need for effective treatment, especially in the elderly population [12].

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Acetaminophen and non-pharmacological interventions, e.g., exercise and improvement in joint mechanics, are considered first-line therapies for patients with OA [6,13,14], however, traditional non-steroidal anti-inflammatory drugs (NSAIDs) are also extensively used to treat the pain associated with OA [6,15,16]. However, NSAIDs are linked to an elevated risk of gastrointestinal (GI) toxicity due to their inhibition of cyclooxygenase-1 (COX-1) enzyme, and this risk has been shown to increase in a linear fashion with age [6,17].

Etoricoxib is a cyclooxygenase-2 (COX-2) selective NSAID with a higher COX-1 to COX-2 selectivity ratio than the other COX-2 selective NSAIDs (e.g. rofecoxib, valdecoxib, or celecoxib) [18] and a lower risk of GI toxicity compared to traditional NSAIDs [19,20]. Recent long-term randomized placebo-controlled trials have demonstrated an increased risk of myocardial infarction (MI) and cerebral thrombosis with rofecoxib and celecoxib compared with placebo [21,22], and a meta-analysis has indicated that the risk may also apply to the use of high-dose traditional NSAIDs [6,23,24].

Etoricoxib has been well studied in patients with OA where it showed comparable efficacy to traditional NSAIDs

and significantly greater efficacy than placebo [6,19,25-34]. However, most of those results were based on clinical trials, which may not accurately represent daily clinical practice characterized by heterogeneous patient populations, in which patients are switched from one therapy to another without washout of drugs or flare of disease. Compared to the randomized controlled trials, observational studies carried out in "real-life" clinical settings provide a more general insight [25,35,36].

Etoricoxib has the potential for wider use as pain relief in the increasing elderly population. Our aim was to examine the efficacy, safety, and tolerability of once-daily dosing of etoricoxib in extremely elderly patients with chronic pain due to OA, in a "real-life" clinical setting.

MATERIALS AND METHODS

Patients

This study was approved by our Institutional Review Board (NO. SE12321), and all patients gave their signed informed consent to participate in the study.

A prospective, single-center, single-arm study was conducted at Yunlin Veterans Nursing Institution, enrolling 19 extremely elderly men with OA (>75 years), who responded inadequately to NSAIDs or other analgesics. The inclusion criteria were as follows: 1) male patients with OA over 75 years of age; 2) Barthel index of Activities of Daily Living (ADL) ≤65; 3) visual analogue scale (VAS) pain score at baseline ≥40; and 4) treatment of pain with NSAIDs (except etoricoxib) or opioids for at least 4 weeks without adequate pain relief.

Methods

The patients were switched to etoricoxib, 60 mg once daily for 4 weeks [37], without prior medication washout. The primary endpoint was the average improvement in the pain index after 4 weeks of etoricoxib treatment, assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) after walking on a flat surface and compared to the baseline pain VAS scores. Other endpoints included average pain improvement assessed by the Brief Pain Inventory Short Form (BPI-SF), average patient satisfaction determined by the Treatment Satisfaction Questionnaire for Medication (TSQM), average improvement in health-related quality of life measured by the Short Form 36 (SF36), and the European Quality of Life-5 Dimensions (EQ-5D). The safety and tolerability were assessed by collecting adverse events data during the 4-week treatment period and the subsequent 2-month follow-up.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY). Continuous and ordinal data with normal distribution were summarized as mean ± standard deviation with range (minimum to maximum). If data were not normally distributed, results were presented as median and minimum-maximum range. Categorical data were presented as frequencies. The differences before and after the treatment were tested using the Wilcoxon signed-rank test, as the data were either of ordinal type or were not normally distributed. All statistical assessments were two-tailed and considered statistically significant at $p < 0.05$.

RESULTS

Demographic and clinical characteristics of 19 extremely elderly men with OA are presented in Table 1. The mean age was 85.9 ± 3.9 years with a min-max range of 79-96 years. The following comorbidities were observed among the 19 patients: hypertension, benign prostatic hyperplasia, diabetes mellitus, dementia, chronic obstructive pulmonary disease, arrhythmia, Parkinson's disease, and asthma (Table 1).

Table 2 shows the WOMAC results before and after the etoricoxib treatment. The WOMAC included 3 domains: pain assessment, stiffness, and disability. The scores for both pain

TABLE 1. Clinical and demographic characteristics of extremely elderly patients

Variables	N=19
Age, years	85.9±3.9 (range: 79-96)
Gender, male	19
Experience of severe disease/pain	
Self	12
Family	7
Cigarette smoking	
Current smoker	1
Former smoker	6
Never	12
Employment status	
Employed or self-employed	1
Retired	12
Other	6
Educational level	
Primary school	1
Middle and high school	18
College and above	0
Comorbidity	
Hypertension	17
BPH	11
Diabetes mellitus	6
Dementia	4
COPD	2
Arrhythmia	2
Parkinson's disease	1
Asthma	1

Age was expressed as mean±SD (range: minimum-maximum), and other categorical variables as frequencies. BPH: Benign prostatic hyperplasia; COPD: Chronic obstructive pulmonary disease

and disability were, on average, lower after the treatment with etoricoxib [$p \leq 0.001$ for pain; $p = 0.020$ for disability] (Table 2).

The BPI-SF results before and after etoricoxib treatment were expressed in percentages and shown in Table 3. The BPI-SF assessed pain severity, pain interference, and pain relief. The average pain and pain right now scores were lower after the treatment ($p = 0.036$ and $p = 0.013$, respectively). Moreover, significant differences were determined in walking and performing normal work before and after the treatment ($p = 0.021$ for walking and $p = 0.030$ for normal work). The average pain relief scores increased from 49.41% to 66.92%; however, the increase failed to reach significance [$p = 0.195$] (Table 3).

The TSQM results before and after the treatment are shown in Table 4. The TSQM included four domains, i.e., effectiveness, side effects, convenience, and global satisfaction. On average, there was a significant increase in the number of patients who reported global satisfaction after the treatment, but not in the number of those who reported effectiveness or convenience of the treatment (Table 4).

Table 5 shows the results of SF36 before and after the treatment. The SF36 included questions related to physical and mental health. A significant improvement after the treatment was noted in 7 of 11 SF36 items, including item #1 (general health, $p = 0.032$), #4 (problems with work or other regular daily activities, $p = 0.026$), #5 (interference with normal social activities due to physical health or emotional problems, $p = 0.017$), #6 (social functioning, $p = 0.008$), #7 (bodily pain severity, $p = 0.009$), #8 (interference with normal work due to physical health or emotional problems, $p = 0.013$), and #10 (interference with social activities due to physical health or emotional problems, $p = 0.038$).

Table 6 shows the results of EQ-5D before and after the treatment with etoricoxib. The EQ-5D included 6 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and VAS. The results showed significantly higher average VAS scores after the treatment ($p = 0.036$). There were no significant changes in the other domains [all $p > 0.05$] (Table 6).

No adverse events occurred during the study period, including 4 weeks of the drug use and at least 2 months of follow-up.

DISCUSSION

Our study showed that after switching to etoricoxib, the pain, joint function, quality of life, and treatment satisfaction improved significantly in the extremely elderly patients with OA. On average, both pain and disability scores decreased as determined using the WOMAC index and BPI-SF. The TSQM results showed a higher perception of overall satisfaction with the treatment among the patients. The quality of life scores measured by the SF36 and EQ-5D VAS also significantly improved after switching to etoricoxib. No adverse

TABLE 2. Comparison of WOMAC scores before and after treatment with etoricoxib

WOMAC	Before etoricoxib		After etoricoxib		*p*
	Median	Range: minimum-maximum	Median	Range: minimum-maximum	
Pain	18	(0-35)	4	(0-24)	<0.001*
Disability	80.5	(0-147)	38.5	(0-134)	0.020*
Stiffness	4	(0-20)	2	(0-12)	0.068

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. The *p* value was calculated using Wilcoxon Signed-rank test. *$p<0.05$ indicates a significant difference

TABLE 3. Comparison of BPI-SF results before and after treatment with etoricoxib

BPI-SF	Before etoricoxib		After etoricoxib		*p*
	Mean ± SD	Range: minimum-maximum	Mean ± SD	Range: minimum-maximum	
Pain severity					
Worst pain	3.37 ± 2.24	(0-7)	2.16 ± 1.80	(0-6)	0.072
Least pain	1.42 ± 1.39	(0-5)	1.11 ± 1.15	(0-4)	0.429
Average pain	2.68 ± 1.86	(0-6)	1.58 ± 1.47	(0-5)	0.036*
Pain right now	2.63 ± 2.48	(0-7)	0.90 ± 1.10	(0-4)	0.013*
Pain interference					
General activities	2.26 ± 2.35	(0-8)	1.50 ± 1.42	(0-5)	0.309
Mood	2.00 ± 1.80	(0-6)	1.06 ± 1.39	(0-4)	0.102
Walking	4.26 ± 3.38	(0-10)	1.72 ± 2.08	(0-6)	0.021*
Normal work	4.42 ± 3.83	(0-10)	1.67 ± 1.82	(0-6)	0.030*
Relation with others	2.26 ± 2.81	(0-10)	1.17 ± 1.76	(0-6)	0.182
Sleep	2.05 ± 2.39	(0-8)	1.11 ± 1.71	(0-6)	0.344
Enjoy of life	2.58 ± 2.14	(0-7)	1.17 ± 1.69	(0-6)	0.092
Pain relief	49.41 ± 28.83	(10-90)	66.92 ± 30.11	(20-100)	0.195

The *p* value was calculated using Wilcoxon Signed-rank test. *$p<0.05$ indicates a significant difference. BPI-SF: Brief Pain Inventory Short Form

TABLE 4. Comparison of TSQM results before and after treatment with etoricoxib

TSQM	Before etoricoxib		After etoricoxib		*p*
	Median	Range: minimum-maximum	Median	Range: minimum-maximum	
Effectiveness	66.67	(33.33-83.33)	66.67	(5.56-100)	0.632
Side effects	ND		ND		
Convenience	66.671	(61.11-100)	72.22	(61.11-100)	0.159
Global satisfaction	75	(16.67-91.67)	79.17	(41.67-133.33)	0.011*

The *p* value was calculated using Wilcoxon Signed-rank test. *$p<0.05$ indicates a significant difference. ND: Not derived; TSQM: Treatment Satisfaction Questionnaire for Medication

TABLE 5. Comparison of SF36 results before and after treatment with etoricoxib

Item#	SF36	Before etoricoxib		After etoricoxib		*p*
		Frequency or mean±SD	Range: minimum-maximum	Frequency or mean±SD	Range: minimum-maximum	
121	In general, would you say your health is:					0.032*
	Excellent	0		2		
	Very good	5		8		
	Good	1		2		
	Fair	11		5		
	Poor	2		2		
2	Compared to 4 weeks ago, how would you rate your health in general now?					0.792
	Much better now	1		1		
	Somewhat better now	2		4		
	About the same	16		13		
	Somewhat worse now	0		1		
	Much worse now	0		0		
3	Does your health now limit you in these activities?	18.47±5.91	(10-30)	15±5.76	(10-26)	0.059
4	During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	5±1.49	(4-8)	6.26±1.85	(4-8)	0.026*
5	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	4.11±1.37	(3-6)	5.16±1.21	(3-6)	0.017*
6	During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?					0.008*
	Not at all	5		11		
	Slightly	6		6		
	Moderately	5		1		
	Quite a bit	3		1		
	Extremely	0		0		
7	How much bodily pain have you had during the past 4 weeks?					0.009*
	None	2		5		
	Very mild	3		10		
	Mild	9		1		
	Moderate	3		3		
	Severe	2		0		
8	During the past 4 weeks, how much did pain interfere with your normal work?					0.013*
	Not at all	2		9		
	A little bit	8		5		
	Moderately	4		4		
	Quite a bit	1		1		
	Extremely					
9	During the past 4 weeks, how you feel and how have things been with you?	36.63±0.64	(32-39)	36.95±3.32	(31-45)	0.876

(Contd...)

TABLE 5. (*Continued*)

Item#	SF36	Before etoricoxib		After etoricoxib		*p*
		Frequency or mean±SD	Range: minimum-maximum	Frequency or mean±SD	Range: minimum-maximum	
10	During the past 4 weeks, how much the time has your physical health or emotional problems interfered with your social activities?					0.038*
	All the time	1		2		
	Most of the time	7		2		
	Some of the time	6		7		
	A little of the time	5		8		
11	How true or false are the statements for you?	12.21±1.18	(10-14)	12.37±1.95	(10-18)	0.749

The *p* value was calculated using Wilcoxon Signed-rank test. *$p<0.05$ indicates a significant difference. SF36: Short form 36

TABLE 6. Comparison of EQ-5D results before and after treatment with etoricoxib

EQ-5D	Before etoricoxib	After etoricoxib	*p*
	Frequency	Frequency	
Mobility			0.132
No problem	8	12	
Mild problem	10	7	
Severe problem	1	0	
Self-care			0.477
No problem	9	13	
Mild problem	8	3	
Severe problem	2	3	
Usual activities			0.374
No problem	8	10	
Mild problem	5	6	
Severe problem	6	3	
Pain/discomfort			0.285
No problem	10	13	
Mild problem	8	6	
Severe problem	1	0	
Anxiety/depression			0.317
No problem	13	15	
Mild problem	5	4	
Severe problem	1	0	
EQ-VAS (median [range: minimum-maximum])	60 (38-93)	90 (50-100)	0.036*

The *p* value was calculated using Wilcoxon Signed-rank test. *$p<0.05$ indicates a significant difference. EQ-5D: European Quality of Life-5 Dimensions; EQ-VAS: European Quality of Life Visual Analogue Scale

events were reported during the 4-week treatment or 2-month follow-up.

This study is the first analysis of the efficacy of etoricoxib in treating OA in the extreme elderly population. The extreme elderly are a growing population, often not adequately represented in epidemiological studies [12]. To the best of our knowledge, there were no previous cohort studies investigating the effect of medication on relieving pain due to OA in the extreme elderly. According to the World Health Organization, an aging society is one in which 7% of the population is ≥65 years old, while in an "aged society" or "hyper-aged society" this proportion reaches 14% and 20%, respectively [38]. Accommodating the aging population is a global challenge [39] and the real-world experience is becoming more and more important.

In a number of trials, the clinical efficacy of etoricoxib in the symptomatic treatment of OA pain has been well documented [6,19,25-34]. The efficacy of etoricoxib treatment of 6-12 weeks was significantly more higher than placebo in improving pain symptoms in patients with OA, and as effective as diclofenac, ibuprofen, naproxen, or celecoxib [26]. Similar to our findings, an analysis of the extreme elderly in a paired design showed reductions in scores for WOMAC pain and physical function and patient's global assessment that were equivalent for 30 mg etoricoxib once daily versus 800 mg ibuprofen 3 times daily, as well as for 60 mg etoricoxib once daily versus 50 mg diclofenac 3 times daily and versus 500 mg naproxen twice daily, and met the criteria for noninferiority for etoricoxib versus celecoxib [26]. Furthermore, efficacy with etoricoxib was maintained for up to 4.5 years in extension studies [40]. Also, etoricoxib was generally well tolerated in clinical trials of patients with OA and other types of arthritis [26]. We observed an improvement of the quality of life in the extremely elderly

patients, with the given treatment dose and period that was shorter compared to the other trials.

In addition to the improvement of the quality of life, drug safety is another important issue. Regarding the risk of thrombotic cardiovascular (CV) events, the multinational etoricoxib and diclofenac arthritis long-term program, including a pooled analysis of >34,000 patients with OA or rheumatoid arthritis, showed that, in terms of the overall rate of arterial and venous thrombotic CV events, etoricoxib was noninferior to diclofenac [19]. Similarly, in a pooled analysis of 12 trials no difference between etoricoxib and non-naproxen NSAIDs was evident regarding thrombotic events [26]. In addition, MI resulting from etoricoxib was reported in only one trial (relative risk 1.58, 95% confidence interval 0.06 to 38.66) [41]. On the other hand, Savage [4] suggested that, due to their thrombotic potential, COX-2 inhibitors are contraindicated in patients with ischemic heart disease or stroke as well as in patients that are at high risk of developing those conditions [4], which was also suggested in another study [42].

Currently, there are several families of drugs clinically recognized as pain therapeutics, which have varying degrees of efficacy and adverse events, often limiting their utility. The management of inflammatory conditions typically includes NSAIDs, inhibitors of COXs (COX-1 and/or COX-2) [43-45], and opiates [43,46]. Significant effort and investment have been made in the development of novel therapeutics for managing pain [43,47,48], including COX inhibiting nitric oxide donors and the dual COX/lipoxygenase (LOX) inhibitor, licofelone. Initial results suggest that those therapies may be more tolerable compared to NSAIDs and selective COX-2 inhibitors [49]. Future clinical trials evaluating the efficacy of new therapeutics in comparison with etoricoxib are warranted, especially in the frail and extremely elderly patients who are at increased risk for side effects and reduced drug tolerance.

Our study has several limitations, including the small number of, only male, patients (n = 19) and single-center design. We included only male patients because the study was conducted at the Yunlin Veterans Nursing Institution where all residents are male veterans. In addition, improvement in health-related quality of life was assessed using only the SF36 and EQ-5D. Other scales, such as the instrumental activities of daily living (IADL) scale [50], could have been used to reflect improvement in daily functioning. Our results showed that, in this extreme elderly population, etoricoxib could relieve pain effectively, but significant improvements in function and ability to do normal work could not be expected due to the impact of patient age and advanced degenerative changes. Other assistance and therapies should be considered, in addition to pharmacologic treatment, in an effort to further aid the patients in this age group.

CONCLUSION

In extremely elderly patients with OA, the pain, joint function, quality of life and treatment satisfaction improved significantly with etoricoxib administration.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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