

International Conference and Exhibition on Pharmacognosy, Phytochemistry & Natural Products

October 21-23, 2013 Radisson Blu Plaza Hotel, Hyderabad, India

Anti-inflammatory activities and the safety of curcuminoid from *Curcuma domestica* Val. rhizome extract compared to Diclofenac sodium for the treatment of Osteoarthritis. A clinical and laboratory investigation on the inflammatory responses in synovial fluid of Knee Osteoarthritis

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Introduction: Osteoarthritis (OA) causes a great burden. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common drug given worldwide. This type of drug can only reduce inflammation and pain, but cannot inhibit the natural history of OA. Curcuminoid is a secondary metabolite found in *Curcuma domestica* and *Curcuma xantorrhyza*, the type of curcuma that people commonly use as spices and a component of herbal medicine. The anti-inflammatory mechanism of curcumin is through three pathways: suppresses cyclo-oxygenase (COX) enzyme activity, suppresses lipo-oxygenase enzyme activity and play a role as free radical scavenger. Monocytes play a significant role in initiating the inflammatory process and antigen elimination. Two important mediators produced by monocytes are COX-2 enzyme and reactive oxygen intermediates (ROI).

Aims: To learn the anti-inflammatory activities and safety of curcuminoid from *Curcuma domestica* Val. rhizome extract compared to diclofenac sodium for osteoarthritis treatment.

Method: The design of this study was prospective randomized open end blinded evaluation (PROBE), including 80 patients suffering from knee osteoarthritis (39 patients got 30 mg three times daily of curcuminoid from *Curcuma domestica* Val. extract for 28 days and 41 patients got 25 mg three times daily of diclofenac sodium for 28 days). The severity of pain was assessed by visual analogue scale (VAS). Synovial fluid analysis was done to compare the anti-inflammatory potency between the two drugs. Adverse events during the study were also noted.

Results: Changes of variables before and after administration of curcuminoid were: COX-2 secretion by synovial fluid monocytes 1.84±0.37 vs 1.15±0.28 respectively (p<0.001), ROI secretion by synovial fluid monocytes 2.23±0.22 vs 0.76±0.30 respectively (p<0.001), synovial fluid leucocyte count 1373.53±597.15/mm3 vs 1199.27±604.23/mm3 respectively (p<0.001), synovial fluid MDA level 1.26±1.13 u.mol/ml vs 0.63±0.46 u.mol/ml respectively (p<0.001), VAS score 54.62±25.25 mm vs 20.85±19.57 mm respectively (p<0001). Changes of variables before and after administration of diclofenac sodium were: COX-2 secretion by synovial fluid monocytes 1.79± 0.38 vs 1.12±0.27 respectively (p<0.001), ROI secretion by synovial fluid monocytes 2.21±0.20 vs 0.75±0.32 respectively (p<0.001), synovial fluid leucocyte count 1257.69±628.36/mm³ vs 1093.59±633.88/mm³ respectively (p<0.001), synovial fluid MDA level 1.01±0.93 u.mol/ml vs 0.57±0.14 u.mol/ml respectively (p<0.001), VAS score 51.39±24.26 mm vs 21.85±16.83 mm respectively (p<0001). The reduction of COX-2 secretion by synovial fluid monocytes in curcuminoid and diclofenac treatments were 0.70±0.51 and 0.67±0.45 respectively (p=0.89). The reduction of ROI secretion by synovial fluid monocytes in curcuminoid and diclofenac treatments were 1.48±0.44 and 1.46±0.42 respectively (p=0.92). The reduction of synovial fluid leucocytes count in curcuminoid and diclofenac treatments were 174.27±78.93 and 164.10±50.91 respectively (p=0.52). The reduction of synovial fluid MDA level in curcuminoid and diclofenac treatments were 0.63 ± 0.43 and 0.44 ± 0.87 respectively (p=0.29). The reduction of VAS score in curcuminoid and diclofenac treatments were 33.76±21.73 and 29.54±21.57 respectively (p=0.23). Number needed to treat for COX-2 secretion was 9, for ROI secretion was 9, for the reduction of synovial fluid leucocyte count was 143, for the reduction of synovial fluid MDA level was 72 and for the reduction of VAS score was 17. There was no significant differences of adverse events during the study in both groups, eitherhead, chest, gastrointestinal tract or urinary tract complaints. Number needed to harm for headache was 500, for palpitation was 42, for dyspneu was 42, for nausea was 21, for diarrhea was 42, and for urinary complain was 500.

Conclusion: Administration of 30 mg three times daily of curcuminoid from *Curcuma domestica* Val. extract significantly reduced the secretion of COX-2 and ROI by synovial fluid monocytes, leucocyte count, MDA level and joint pain score, while no significant difference compared to 25 mg three times daily of diclofenac sodium treatment. There was no significant difference in adverse events during the study in both groups, either on head, chest, gastrointestinal tract or urinary tract complaints.