Comparing two low doses (5mg and 10mg) of prednisolone in short term treatment of painful hand osteoarthritis: A placebo controlled, double blind randomized trial.

Singh Surjeet, Singh Jatinder

Abstract:

Objective: To find out the safety and efficacy of two low doses (5mg and 10mg) of prednisolone in painful hand osteoarthritis compared to placebo.

Methods: This is a prospective, randomized, double-blind, placebo controlled trial of patients fulfilling the American College of Rheumatology (ARC) criteria hand osteoarthritis. Participants were divided into three groups after proper randomization, and each group received tablet 5mg prednisolone, tablet 10mg prednisolone or a matched tablet of placebo daily for six weeks with proper tapering of dose for next two weeks. Patients were re-evaluated at 6 and 12 weeks for painful, swollen and tender joint counts; early morning stiffness; AUSCAN pain, stiffness and function VAS; and radiographic changes in both hands joints.

Results: Out of 32 patients included in the study, 11 were administered prednisolone 10mg, another 11 were administered prednisolone 5mg, and 10 were administered placebo after proper randomization. After 6 and 12 weeks, there was a definite reduction in AUSCAN pain, stiffness and function VAS scores; early morning stiffness; painful, tender, and swollen joint counts, and radiological changes in joints in all the three groups, but difference was not statistically significant between the groups.

Conclusion: Low dose prednisolone (5mg and 10mg) is not more effective than placebo in painful hand osteoarthritis. However, further studies with sufficient sample size are recommended to find out its efficacy and safety in painful hand osteoarthritis, or to substantiate our findings.

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Introduction

Osteoarthritis is a chronic disease of joints, characterized by destruction of articular cartilage, overgrowth of bone with lipping and spur formation, and impaired function. It is prevalent in 20% of adult population[1,2]. Hand osteoarthritis is particularly burdensome and common, with a prevalence of 16% in adult population, and, which may increase to 26% in > 70yrs old female population[3,4]. Therefore, its prevalence as well as its worse effect on quality of life increases with increasing age[5,6].

Treatment options for painful hand osteoarthritis include both non-pharmacological like education and exercise, as well as pharmacological. Pharmacological options are limited to simple analgesics, NSAIDS, and injectable corticosteriods[7,8,9,10]. Their effect is moderate. Moreover, NSAIDS are associated with significant toxicity particularly in elderly patients, and injectable corticosteroids are not feasible in every patient. Present pharmacological treatment of painful hand osteoarthritis is based on the idea that, in addition to mechanical triggers, local inflammation is the source of pain and radiological damage progression in painful hand osteoarthritis[11]. Furthermore, radiological studies show high prevalence of synovitis in painful hand osteoarthritis[12,13].

Author Affiliations
Singh Surjeet,
Associate Professor, Department of Clinical Pharmacology
SKIMS Srinagar
Singh Jatinder,
MS (Orthopedics) , J&K Health services

Correspondence:
Singh Surjeet,
Associate Professor, Department of Clinical Pharmacology
SKIMS Srinagar
Email: surjit.singh@skims.ac.in
M: 97977-30444

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Key Words: :
Painful hand osteoarthritis; Prednisolone; Visual analogue scale.

Corticosteroids are potent, multi-targeted anti-inflammatory drugs. While searching for the evidence on short term oral corticosteroid treatment efficacy and safety, we came across two important placebo-controlled randomized trials. One trial show that low dose oral prednisolone (5mg once daily for 4 weeks) did not gave significant relief of pain compared to placebo[14], whereas another randomized placebo-controlled trial carried out across two centers in Netherlands[11] show a good effect of low dose oral prednisolone (10mg once daily for 6 weeks) in both relieving pain and improving signs of inflammation. Both studies were based on the evidence based idea[13] that local inflammation is the cause of pain in painful hand osteoarthritis. So, we carried out present study to show whether there is really any significant difference in two low doses (5mg and 10mg) of corticosteroids in providing pain relief in painful hand osteoarthritis, keeping in mind the same basis that local inflammation is source of pain in this condition.

Material and Method

This was a prospective, randomized, double-blind, placebo-controlled trial. Patients fulfilling the American College of Rheumatology criteria[15] were included in the study after getting proper written informed consent. Also, patients having signs of inflammation in their distal and proximal interphalangeal joints, self-reported hand pain with at least 40/100 mm on hand pain visual analogue score, and previous or at baseline radiograph showing Kellgren-Lawrence score of at least 1 were also included in the study.

Any inflammatory arthritis, patients with positive rheumatoid factor, sensitivity to prednisolone, recent pregnancy, uncontrolled diabetes or hypertension, active infection, osteoporosis, psoriasis and cancers were excluded from the study.

After proper randomization, patients were divided into three groups. One group (group I) was administered prednisolone 10 mg once daily, another group (group II) a matched capsule of prednisolone 5 mg once daily, and group III was administered again a matched capsule, but of placebo, for a period of 6 weeks, with proper tapering of dose for next two weeks. Patients who were already taking analgesics (NSAIDS) for pain relief were asked to continue with their medication.

After proper clinical history and thorough general and systemic clinical examination, baseline characteristics of all the three groups were noted. Baseline characteristics in addition to general characteristics and demographic profile included:

1. Examination of metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints for:
   - Painful, swollen and tender joint counts

Painful joints: patient reported pain within last 48 hrs.

Tender joints on palpation: pressure applied until assessors nail blenched

Swollen joint: soft tissue swelling

2. Completion of VAS version of AUSCAN hand osteoarthritis index[16]
3. Early morning stiffness
4. Radiography of both hands, with damage assessed with Kellgren-Lawrence scoring[17]

Patients were followed up at 6 and 12 weeks, with all above parameters repeated at each follow up visit.

Results

52 patients were screened, out of which only 32 patients fulfilled the inclusion criteria and were included in the study. After proper randomization, 11 patients were administered prednisolone 10 mg once daily (Group I), another 11 patients were administered prednisolone 5 mg once daily (Group II) and 10 patients were administered placebo (Group III). Baseline characteristics of these patients are given in Table 1.

Table 1. Baseline characteristics of patients:

Parameters	Group I (n=11)	Group II (n=11)	Placebo (n=10)
Age (yrs) mean(sd)	58 (8)	60 (7)	61 (9)
Sex n (%) M F	 4 (36.3%) 7 (63.6%)	 5 (45.4%) 6 (54.5%)	 3 (30%) 7 (70%)
Duration of disease (years) median	6.5 (3-10)	6 (4-9)	6.2 (2.5-8)
Body mass index mean (sd)	27.3 (5.8)	27.6 (4.6)	27.5 (5.2)
NSAID usage n(%)	7 (63.6%)	5 (45.4%)	7 (70%)
Early morning stiffness (mns.) median	62 (30-120)	60 (35-150)	61 (40-140)
Painful joint count (0-28) median	6 (4-8)	7 (5-11)	6 (3-8)
Tender joint count (0-28) median	5 (3-8)	5 (4-12)	5 (4-8)
Swollen joint count (0-28) median	2 (0-3)	2 (1-4)	1 (1-5)
AUSCAN pain VAS mean (sd)	58 (15)	62 (16)	60 (16)
AUSCAN stiffness VAS mean (sd)	56 (21)	55 (30)	55 (28)
AUSCAN function VAS mean (sd)	61 (16)	60 (23)	60 (21)
Joint radiographic osteoarthritis global scoring (range 0-32) mean(sd)	19 (6)	21 (7)	20 (6)
Erosive arthritis n(%) No. of patients with even one joint in Verbruggen-Veys erosive or remodeling phase	4 (36.3%)	3 (27.2%)	3 (30%)
Kellgren-Lawrence sum score (0-120) mean(sd)	32 (15)	30 (14)	31 (16)

Concomitant treatment:

At 6 weeks, 2 (28.5%) out of 7 patients taking NSAIDS altered the NSAIDS intake in group I, i.e. they reduced the NSAIDS intake. There was no

change in NSAIDS intake in patients of group II and group III. At 12 weeks, none of the patients reduced the NSAIDS intake (dose or frequency of intake), while three patients (one (20%) from group II and 2 (28.5%) from group III out of those taking NSAIDS in these respective groups) increased the dose of NSAIDS intake.

Clinical and Radiological parameters:

At 6 weeks, there was a definite improvement in AUSCAN pain, stiffness and function VAS scores; early morning stiffness; painful, tender and swollen joint counts, and radiographic parameters (joint radiographic osteoarthritis global scoring and Kellgren-Lawrence sum score) when compared to baseline; but this decrease was not statistically significant in any of the three groups. When three groups were compared (between group comparison) again there was no statistically significant difference observed Table 2.

Table 2: Clinical and Radiological parameters at 6th week.

Parameters	Group I	Group II	Group III	F-ratio	p-value
AUSCAN pain VAS	-17 (-24; -12)	-15 (-18; -6)	-12 (-20; -6)	1.6	0.21
AUSCAN stiffness VAS	-14 (-24; 5)	-10 (-17; -3)	-7 (-21; -6)	0.52	0.46
AUSCAN function VAS	-11 (-16; -4)	-9 (-14; -2)	-8 (-15; -6)	0.21	0.61
Early morning stiffness	-18 (-36; -15)	-15 (-38; -10)	-8 (-51; 12)	1.2	0.2
Painful joint count	-1 (-3 ; 2)	-1 (-2 ; 2)	0 (-1 ; 3)	0.86	0.44
Tender joint count	-2 (-4 ; 1)	-1 (-2 ; 3)	-1 (-1 ; 2)	1.81	0.3
Swollen joint count	-1 (-2 ; 1)	-1 (-3 ; 2)	0 (-2 ; 2)	1.61	0.26
Joint radiographic osteoarthritis global scoring	-4 (-6; 1)	-3 (-4; 2)	-1 (-2; 3)	3.02	0.12
Kellgren-Lawrence sum score	-8 (-10; 2)	-6 (-10; 3)	-3 (-4; 6)	1.52	0.28

At 12 weeks, again there was an apparent decrease in many of the clinical as well as radiological parameters compared to baseline, which again was not statistically significant. When three groups were compared, no statistically significant difference was observed between three groups. Table 3.

Table 3: Clinical and Radiological parameters at 12th week.

Parameters	Group I	Group II	Group III	F-ratio	P-value
AUSCAN pain VAS	-11 (-16; 1)	-9 (-15; 0)	-8 (-16; -3)	1.32	0.26
AUSCAN stiffness VAS	-8 (-18; -2)	-8 (-16; -1)	-6 (-17; 2)	0.06	0.82
AUSCAN function VAS	-9 (-17; 1)	-7 (-18; 1)	-5 (-14; 3)	0.27	0.60
Early morning stiffness	-12 (-30; 10)	-8 (-24; 6)	-8 (-30; 5)	0.89	0.35
Painful joint count	-1 (-1; 2)	0 (-2; 3)	1 (-1; 3)	0.01	0.94
Tender joint count	0 (-6; 2)	1 (-3; 3)	1 (-1; 4)	0.63	0.43
Swollen joint count	-1 (-3; 2)	1 (-5; 3)	2 (-2; 3)	0.74	0.33
Joint radiographic osteoarthritis global scoring	-3 (-4; 2)	-2 (-3; -1)	-1 (-2; 2)	0.38	0.54
Kellgren-Lawrence sum score	-4 (-11; -3)	-2 (-6; 2)	1 (-8; 6)	0.09	0.77

Adverse effects:

Most of the observed effects were mild type. Weight gain, headache and infections were seen more with prednisolone 10mg (group I). Headache, muscle aches and pains and infections were observed with prednisolone 5mg (group II) as well as with placebo (group III). Hyperglycemia and glaucoma was observed in one (9%) patient each from group I. There was no statistically significant difference observed between three groups regarding adverse effects. Table 4.

Table 4: Adverse effect profile:

Adverse effects	Group I	Group II	Group III	X^2
Weight gain	2 (18.1%)	1 (9%)	1 (10%)	0.48
Headache	2 (18.1%)	3 (27.2%)	2 (20%)	0.29
Muscle aces and pains	1 (9%)	2 (18. 1%)	2 (20%)	1.12
Glaucoma	1 (9%)	0	0	1.96
Sleep disorders	0	1 (9%)	1 (10%)	1.08
Infections	2 (18.1%)	2 (18.1%)	2 (20%)	0.0116
Hyperglycemia	1 (9%)	0	0	1.96

Significant X2 >5.99-(p<0.05)

Discussion

This prospective randomized, double blind placebo controlled trial comparing two doses of prednisolone (10mg vs. 5mg) show substantial improvement in pain control and other clinical and imaging parameters in painful hand osteoarthritis when compared to baseline in all the three groups. But there was no statistically significant difference observed when three groups were compared. These results are consistent with previous randomized placebo controlled trial[14] where prednisolone 5mg was compared with placebo. In both case, placebo group also showed better improvement in symptoms. This is already shown in a recent meta-analysis[18] that placebo effect is definite in osteoarthritis trials. A systemic literature review [19] of placebo controlled trials has also sown negative results of intra-articular glucocorticoids in patients with thumb-base-osteoarthritis. However, the thumb-base-osteoarthritis is a distinct hand osteoarthritis subset requiring a distinct approach as reported by Kloppenburg M et.al.[20]

A placebo-controlled study[21] , where combination of prednisolone (3mg) plus dipyridamole (200-400mg), was administered, has shown improvement in symptoms compared to placebo. However, these improvements were at the cost of more study withdrawals because of adverse events (mostly headache). Furthermore, inclusion criteria of this study (swollen joints, moderate to severe radiological osteoarthritic changes) were different from our study which focused mostly on milder radiographic changes, and did not included

swollen joints as mandatory in inclusion criteria.

Results of our study somewhat show that, inflammatory changes may not be only source of pain in painful hand osteoarthritis. This view gets support from a recent randomized double-blind trial[22], where a very effective anti-inflammatory anti-TNF therapy, although has shown better structure modification in terms of reduced joint erosion progression, there was no statistical reduction in symptoms of hand osteoarthritis. This is in contradiction to the results of a recent trial[23] which identifies MRI-confirmed bone marrow changes, erosion and bone attrition (all inflammatory changes) as potential peripheral sources of nociceptive pain in hand osteoarthritis. Furthermore, negative findings of anti-TNF therapy may be because, targeting a single cytokine might not be sufficient in treating osteoarthritis, because plenty of them have been documented to play their role in osteoarthritis[19,24].

A recent double-blind, randomized controlled trial11 of prednisolone 10mg for 6 weeks, has shown a substantial reduction in finger pain and better improvement in other secondary outcomes (e.g. OMERACT-OARSi responder criteria; scores on AUSCAN pain and functional scales; Michigan Hand outcome questionnaire scores etc.) compared to placebo. MRI and ultrasound measures also showed signs of decreased inflammation. Results of the study are in contrast to our study. Reason can be that, while above trial was more powerful , with sufficient sample size from two sites in Netherlands, ours was a small sample-sized study, not powerful enough to find a significant difference between two doses (10mg and 5mg) of prednisolone and placebo. Therefore, further studies with sufficient sample size are recommended to find out whether prednisolone can be effective and safe remedy in painful hand osteoarthritis.

Conclusion

Two low doses of prednisolone (5mg and 10mg) are both not more effective in treatment of painful hand osteoarthritis when compared with placebo. However, further large scale controlled, randomized studies with large sample size are recommended to find out whether prednisolone can be an effective and safe analgesic in painful hand osteoarthritis or to confirm our findings.

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