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# CLINICAL AND METABOLIC EFFECTS OF INTRA ARTICULAR STEROIDS IN RHEUMATOID ARTHRITIS

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## ABSTRACT
**Introduction:** Local steroids have always been considered a safer alternative to systemic steroids. But there are only few Indian studies regarding the metabolic effects of Intra articular steroids (IAS) in patients with rheumatoid arthritis (RA). **Aim & Objectives:** To assess the metabolic effects of intra articular steroids in rheumatoid arthritis patients who had low disease activity but for persistent pain over few joints. **Methodology:** Intra-articular steroids were given to patients with rheumatoid arthritis with low disease activity and a few inflamed joints. Metabolic parameters, disease activity scores (DAS 28, CDAI) and pain score (VAS) were assessed before and after injections (at 2 days and 4 weeks). **Results:** There were significant increases in neutrophil count ($p<0.001$), serum total proteins and globulins ($p<0.05$), decreases in lymphocyte count ($p<0.001$), VAS score for pain ($p<0.001$), systolic and diastolic blood pressure ($p<0.05$) at 2 days. There were significant decreases in CDAI, DAS 28 & VAS scores ($p<0.001$) & ESR($p<0.05$) at 4 weeks. **Conclusion:** There were transient changes in metabolic parameters at 2 days which were not evident at 4 weeks. There was a significant decrease in disease activity and pain at 4 weeks.

**KEYWORDS:** Intra articular steroids (IAS), rheumatoid arthritis (RA).

## INTRODUCTION
Rheumatoid arthritis (RA) is the most common inflammatory arthropathy worldwide affecting all races. It predominantly affects women with a sex ratio between 2:1 and 4:1.[1] It is characterized by the presence of long-standing inflammation of the di-arthrodial joints resulting in symmetric polyarthritis and synovial membrane hypertrophy with progressive joint damage, bone and cartilage destruction as well as deformity.[2]

DMARDS are slow in action and will take 6-8 weeks to start their efficacy. Biologic response modifiers (BRM) are effective but of high cost and are not yet within the financial scope of common man. As a result of which, the time tested corticosteroids are still the wonder drugs in the treatment of RA and are to be used judiciously and rationally.[3]

Oral steroids cause a lot of well-known side effects like diabetes mellitus, hypertension, premature cataracts, osteoporosis or Cushing's syndrome. Hence their use should be limited for the shortest duration possible with the least possible dose. As with others conditions requiring long term steroid administration, local steroids i.e. intra-articular steroid (IAS) injections are an alternative option for providing rapid symptomatic relief of painful swollen joints in patients with rheumatoid arthritis.

Local steroids have always been considered a safer alternative to systemic steroids with few metabolic side effects.[4,5] But the data regarding the metabolic effects of IAS in patients with RA is scarce[6] and there are few Indian studies.

Hence we conducted this study to assess the metabolic effects of intra-articular steroids in Rheumatoid arthritis patients who had the disease under control by drugs except for persistent pain over few joints.

## AIM
To determine the clinical and biochemical effects (viz. alterations in metabolic parameters and improvement in disease activity and pain) of intra-articular steroids in Rheumatoid arthritis patients who had the disease under control by low stable doses of oral steroids / NSAIDS / immune-suppressants except for persistent pain over few joints.

## MATERIALS AND METHODS
**Type of study:** Prospective analytical (Before-after) study.

**Study population**
Patients attending Rheumatology OPD in Tirunelveli Medical College and hospital.

**Sample size:** 50.

**Inclusion criteria**
Patients diagnosed as Rheumatoid arthritis as per the 2010 ACR / EULAR Rheumatoid Arthritis Classification Criteria[7] who had the disease under control by low stable doses of oral steroids / NSAIDS / immunosuppressants except for persistent pain over few joints.

**Exclusion criteria**
Patients diagnosed as Rheumatoid arthritis who had

- pain in many joints.
- local site infection, known hypersensitivity to intra–articular agents, septic joints, unstable joints, prosthetic joints.
- poor glycemic control, uncontrolled hypertension, elevated renal and liver function parameters and elevated cell counts, unstable coagulopathy.
- Patients on oral contraceptives, heparin, thyroxine, bisphosphonates, vitamin D.

**METHODOLOGY**
After obtaining fully informed written consent, under strict aseptic precautions, the joints were aspirated to apparent dryness. After infiltration of local anesthetic agent, they were administered intra-articular Triamcinolone acetonide injection (40mg per ml) in each of the swollen joints (small joints of hand and wrist(0.5 mg/kg body weight), elbow and ankle, knee and shoulder (1 mg/kg body weight) using anatomical landmarks for needle placement.

The following parameters were assessed immediately before and after (2 days & 4 weeks) intra- articular steroid injections:

- FBS, PPBS, Blood pressure, Lipid profile, RFT, LFT, CBC, S. Calcium ALP, Uric acid, ESR, CRP.
- Disease activity Score (DAS 28) and Clinical Disease Activity Index (CDAI) to assess the disease activity and Visual Analogue score (VAS) to assess the pain.

Data was managed on Microsoft Excel and tested on SPSS for windows version15 software. Student's Paired t- test was used for data analysis. Results were considered significant at $p<0.05$.

**RESULTS**
50 patients who satisfied the above criteria were included in the study.

20% were males and 80% were females. Mean age of the patients was 44 years. Among females 45% were in the perimenopausal age group. 25% females had symptoms for 10 years or more.

At baseline: 86% had moderate disease activity, calculated from DAS 28; 6% had high disease activity; while 8% patients were in remission. Whereas according to CDAI, 50% had low disease activity and 50% had moderate disease activity.

**Table 1: Disease activity at baseline based on DAS 28 Score.**

| DAS 28 score | Disease activity | % patients |
|---|---|---|
| <2.6: | Remission | 8 |
| <3.2: | Low | |
| 3.2-5.1 | Moderate | 86 |
| >5.1 | High | 6 |

**Table 2: Disease activity at baseline based on CDAI Score.**

| CDAI | Disease activity | % patients |
|---|---|---|
| ≤2.8 | Remission | |
| >2.8-≤10 | Low | 50 |
| >10-≤22 | Moderate | 50 |

**After 2 days**
There were no significant changes in blood sugar, urea, creatinine, calcium, total count, eosinophils, cholesterol, triglycerides, HDL, LDL, VLDL, hemoglobin, RBC count, platelets, hematocrit, ESR, total bilirubin, direct bilirubin, albumin, ALP, ALT, AST.

There were significant increases in neutrophil count ($p<0.001$), serum total proteins and globulins ($p<0.05$).

There were significant decreases in lymphocyte count ($p<0.001$), VAS score for pain ($p<0.001$), systolic and diastolic blood pressure ($p<0.05$).

**Table 3: Parameters with significant changes at 2 days.**

| Parameter | Mean Value Before Intra-Articular Steroids | Mean Value 2 Days After Intra-Articular Steroids | p VALUE |
|---|---|---|---|
| Neutrophils(cells/cu.mm) | 5827±2297 | 7364±1450 | <0.001 |
| S.Proteins (g/dl) | 6.82±0.45 | 7.07±0.49 | <0.05 |
| S.globulin(g/dl) | 2.72±0.45 | 2.98±0.43 | <0.05 |
| Lymphocytes(cells/cu.mm) | 2690±885 | 2050±945 | <0.001 |
| Systolic BP(mm Hg) | 127.77±19.86 | 116.67±20 | <0.05 |
| Diastolic BP(mm Hg) | 82.22±8.33 | 75.56±11.30 | <0.05 |
| Visual analog score | 5.58±2.60 | 2.58±2.02 | <0.001 |

**After 4 weeks**

There were no significant changes in blood sugar, urea, creatinine, total bilirubin, indirect bilirubin, protein, albumin, globulin, ALT, ALP, AST, cholesterol, TGL, HDL, VLDL, sodium, potassium, calcium, total count, neutrophil, lymphocyte, eosinophil count, platelet, RBCs, hemoglobin, hematocrit, uric acid, blood pressure.

There were significant decreases in pain and disease activity scores: CDAI, DAS 28 & VAS scores ($p<0.001$) & ESR($p<0.05$). There was a 38% fall in ESR at 4 weeks. There was a 54% reduction in VAS pain score at 2 days which remained at 4 weeks (55% reduction).

**Table 4: Parameters with significant changes at 4 weeks.**

| Parameter | Mean Value Before Intra-Articular Steroids | Mean Value 4 Weeks After Intra-Articular Steroids | p VALUE |
|---|---|---|---|
| CDAI | 10.40±4.23 | 4.96±3.98 | <0.001 |
| DAS28 | 4.56±0.92 | 3.15±0.84 | <0.001 |
| VAS score | 5.92±2.55 | 2.64±2.06 | <0.001 |
| ESR (mm/hr) | 54.54±26.50 | 33.88±16.72 | <0.05 |

Considering DAS 28 score, disease activity came down significantly from moderate (86%) to low (53%) and 22% achieved remission at 4 weeks. 38% achieved remission at 4 weeks as per CDAI score.

**Table 5: Changes in disease activity at 4 weeks as per DAS 28 score.**

| DAS 28 score | Disease activity | % patients (AT BASELINE) | % patients (AT 4 WEEKS) |
|---|---|---|---|
| <2.6: | Remission | 8 | 22 |
| <3.2: | Low | | 53 |
| 3.2-5.1 | Moderate | 86 | 22 |
| >5.1 | High | 6 | 3 |

**Table 6: Changes in disease activity at 4 weeks as per CDAI score.**

| CDAI | Disease activity | % patients (AT BASELINE) | % patients (AT 4 WEEKS) |
|---|---|---|---|
| ≤2.8 | Remission | | 38 |
| >2.8-≤10 | Low | 50 | 54 |
| >10-≤22 | Moderate | 50 | 8 |

## DISCUSSION

In the management of rheumatoid arthritis, the old "pyramidal approach" concept has been replaced by the present concept of 'treat-to-target' and achieve early remission/ low disease activity.[8]

Of the 63 currently available RA disease activity measurement tools, we used CDAI, DAS28 which had excellent reliability and validity.[9]

In the CIMESTRA study group[10], at five years, more than 75% of patients were in DAS28 remission. Two weeks after inclusion in the project, 39% were in DAS28 remission.

In our study, 22% achieved DAS28 remission at 4 weeks as per DAS 28 score.

In the study done by Taylor et al[11] in Staffordshire Rheumatology Centre, one week following intra-articular steroid injection, mean drop for ESR was 46% lasting over a variable period up to 6 months. In our study, there was a 38% fall in ESR at 4 weeks.

In the study done by Marshall Godwin et al[12], intra-articular corticosteroids resulted in a clinically and statistically significant reduction in knee pain 1 week after injection that continued for 3 to 4 weeks. In our

study, there was a 55% reduction in VAS pain score at 4 weeks.

Glucocorticoids are known to increase the white blood cell (WBC) count upon their initiation. The increase in WBC count is predominantly neutrophils. This is due to demargination of neutrophils from the endovascular lining, delayed migration of PMNs into tissue and rate of apoptosis and release of immature (bands) neutrophils from the bone marrow into the circulation.[13] Corticosteroids induce lymphopenia (an effect lasting for hours to days) partly by redistribution from blood to tissues and partly by lymphocyte distribution.[14] In line with this, there was a 26% increase in neutrophils and 24% decrease in lymphocytes at the end of 2 days which did not persist at 4 weeks in our study.

Though we expect an increase in blood pressure due to corticosteroid induced sodium and fluid retention, the significant fall in systolic (9%) and diastolic (8%) blood pressure can be accounted by the decreased sympathetic drive due to pain relief following intra-articular steroid injection.

Glucocorticoids may exert a permissive physiological effect on hepatic protein synthesis.[15] In terms of circulating serum hepatic proteins, in experimental animal models glucocorticoids acutely stimulate hepatic protein synthesis, and may enhance immunoglobulin production.[16] Accordingly in our study, there was a 4% increase in serum protein and 10% increase in serum globulin level at 2 days which did not persist at 4 weeks.

## CONCLUSION

Intra – articular steroids cause only transient changes in metabolic parameters and provide persistent decrease in pain and disease activity. Though intra articular steroids are not disease modifying, they are very effective in controlling disease activity in individual joints without causing any metabolic derangement. Hence they can be widely administered to patients to control pain and disease activity over few joints and as bridge therapy before initiating immuno-suppressants without systemic side effects.

## REFERENCES


1. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci., 2006; 1069: 212–22.
2. Amaya-Amaya J, Rojas-Villarraga A, Mantilla RD, et al. Rheumatoid arthritis. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press, 2013 Jul 18. Chapter 24.
3. Kumar P, Banik S. Pharmacotherapy Options in Rheumatoid Arthritis. Clinical Medicine Insights Arthritis and Musculoskeletal Disorders, 2013; 6: 35-43. doi:10.4137/CMAMD.S5558.
4. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. **Clin Sci (Lond),** 1998; 94: 557– 572.
5. MacMahon, P.J., Eustace, S.J., and Kavanagh, E.C. Injectable corticosteroid and local anesthetic preparations: A review for radiologists. Radiology, 2009; 252: 647–661.
6. F. Zulian, G. Martini, D. Gobber, M. Plebani, F. Zacchello, P. Manners; Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial, *Rheumatology*, 1 October 2004; 43(10): 1288–1291.
7. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum, 2010; 62: 2569–81.
8. Londhey.A. Vikram Intra-Articular Steroids in 'Treat-to-Target' Therapy in Early Rheumatoid Arthritis; JAPI August 2014 Volume 62.
9. ANDERSON J, CAPLAN L, YAZDANY J, et al. Rheumatoid Arthritis Disease Activity Measures: American College of Rheumatology Recommendations for Use in Clinical Practice. Arthritis care & research, 2012; 64(5): 640-647. doi:10.1002/acr.21649.
10. L Hetland, Merete & Hørslev-Petersen, Kim. (2012). The CIMESTRA study: Intra-articular glucocorticosteroids and synthetic DMARDs in a treat-to-target strategy in early rheumatoid arthritis. Clinical and experimental rheumatology. 30.
11. Taylor, H.G., Fowler, P.D., David, M.J., Dawes, P.T. Intra-articular steroids (confounder of clinical trials). Clin Rheumatol, 1991; 10: 38–42.
12. Godwin M, Dawes M. Intra-articular steroid injections for painful knees. Systematic review with meta-analysis. Canadian Family Physician, 2004; 50: 241-248.
13. Nakagawa M, Terashima T, D'yachkova Y et al. Glucocorticoid-induced granulocytosis: contribution of marrow release and demargination of intravascular granulocytes. Circulation, 1998; 98: 2307-13.
14. Fauci AS. Mechanisms of corticosteroid action on lymphocyte subpopulations. I. Redistribution of circulating T and b lymphocytes to the bone marrow. Immunology, 1975; 28(4): 669-680.
15. Sato T, Tajiri J, Shimada T, Hiramatsu R, Umeda T. 1984 Abnormal blood chemistry data in Cushing's syndrome: comparison with those for fatty liver. Endocrinol Jpn., 31: 705–710.
16. Heim WG, Ellenson SR. 1965 Involvement of the adrenal cortex in the appearance of rat slow 2 globulin. Nature, 208: 1330–1331.