Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20175074

Original Research Article

Intra articular hyaluronic acid versus intra articular triamcinolone hexacetonide in primary osteoarthritis of knee: a comparative study

Sabeena Kizhedath[1], Gopesh Valoth[2]*, Bindhu Vasudevan[3]

[1]Department of Pharmacology, Govt. Medical College, Ernakulam, Kerala, India
[2]Department of Pharmacology, Govt. Medical College, Thrissur, Kerala, India
[3]Department of Community Medicine, Govt. Medical College, Ernakulam, Kerala, India

Received: 17 October 2017
Revised: 25 October 2017
Accepted: 30 October 2017

***Correspondence to:**
Dr. Gopesh Valoth,
Email: drgopeshvaloth@gmail.com

ABSTRACT

Background: Osteoarthritis (OA) is a painful, chronic disease with widespread burden on patients, communities, social and health care systems. Intraarticular (IA) Hyaluronic acid (HA) and corticosteroids are established treatments for OA knee. However, concerns exist regarding effect, duration, safety, effectiveness across population and heterogeneity. Aim of the study is to compare the efficacy and safety of IA HA with THA in the treatment of primary osteoarthritis knee.
Methods: A descriptive cross-sectional study was done among 30 patients. One group (n=15) received IA THA 20mg/2mL on day 0 and other group (n=15) received IA HA 20mg/2 mL on day 0, 7 and 14 under aseptic precautions. The efficacy assessment using VAS for overall pain, joint line tenderness and 15m walking time in seconds were recorded. Side effects if any were noted.
Results: Comparing both treatments IA THA provided superior short-term pain relief. But HA showed sustained benefit up to six months.
Conclusions: OA being a chronic disease process, we need a drug which has a long-lasting effect. Additive effect of HA and THA can be considered for better efficacy.

Keywords: Hyaluronic acid, Intra-articular, Osteoarthritis, Triamcinolone hexacetonide, Visual analog scale

INTRODUCTION

Osteoarthritis (OA) knee is the most common disease of joints which cause pain and functional limitation in elderly. OA knee presents at an early age in South Asia which is mostly due to working conditions and habits which need squatting.[1] Pain from OA is a key symptom in the decision to see medical care and is an important antecedent to disability.[2] The rapid increase in the prevalence of this already common disease suggests that OA will have a growing impact on health care and public health systems in future.[3]

Viscosupplementation is a novel safe and possibly effective form of local treatment for osteoarthritis.[4] It aims at supplying replacement hyaluronic acid into the joint space to return the elasticity and viscosity of synovial fluid to normal.[5] Hyaluronic acid, a polysaccharide consisting

of long chain of disaccharides is a natural component of cartilage and plays an essential part of viscoelastic properties of the synovial fluid. HA is considered not only a joint lubricant, but also a physiological factor in the trophi status of cartilage. The estimated total hyaluronic acid in a human knee joint is from 4-8mg.[6]

Intra articular injections of hyaluronic acid with a molecular weight between 500 and 750 kilodaltons (kD) have been studied using corticosteroid injections or NSAIDs as control treatment and by conducting placebo controlled trials.[7-11] These studies suggested that intra articular injections of HA may improve the clinical condition and have long term beneficial effect in knee osteoarthritis patients, if osteoarthritis is less than moderate in grade. A review by Maheu looked at 5 different clinical trials, comparing different regimens of Hyalgan versus corticosteroids injections in osteoarthritis knee, with follow ups from 2-12 mths.[12-15]

One study showed initial superiority of Hyalgan and in three studies equal efficacy over time. The fifth study used a combination of Hyalgan and corticosteroid injections initially. The corticosteroid injections seemed to increase the long-term efficacy suggesting that these two combinations would be promising.[16] On the other hand, a double-blind placebo controlled trial involving 91 patients with radiologically confirmed knee osteoarthritis concluded that intraarticular administration of 750 kD of hyaluronic acid offered no significant benefit over placebo during 5week treatment period.[17]

Although accepted as a conservative treatment option for knee OA, the debate about the effectiveness of intra articular treatment of HA is still going on because of contrasting outcomes.[18]

METHODS

This study compares the efficacy and safety of intra articular hyaluronic acid with intra articular Triamcinolone hexacetonide in primary osteoarthritis knee. The study design - descriptive cross- sectional study. Study period was 6 months. Study setting was at Department of Orthopedics and Rheumatology, GMC, Kozhikode.

Study population was 30 patients of either sex with symptoms of osteoarthritis knee were included, who fulfilled the below mentioned inclusion and exclusion criteria. They were divided into two groups of 15 patients.

Inclusion criteria

- Men and women suffering from primary osteoarthritis knee.
- The age group of 40-65 yrs.
- Confirmed by ACR clinical criteria.
- Belonging to radiological grade 1,2 and 3 of Kellgren and Lawrence scale.

Exclusion criteria

- Peptic ulcer and GIT disorders.
- Pregnancy and lactation.
- Diabetes mellitus.
- Intra articular injections and arthroscopy within one year.

Trial method

Patients were alternatively randomized into two groups to receive either hyaluronic acid or triamcinolone hexacetonide. A complete history was elicited using a pretested proforma which included personal data, duration of illness and other modalities of treatment. Radiological evaluation of joint was done using Kellgren and Lawrence scale. The study group received either intra articular triamicinlone hexacetonide 20mg on day 0 or intra articular hyaluronic acid 20mg/2ml on days 0, 7 and 14 under aseptic precautions. The patients were prescribed a course of antibiotic cefadroxil 500mg bid for 5 days. Rescue analgesic was paracetamol 500mg on an SOS basis. Prior to the treatment Visual Analogue Scale (VAS) for overall pain, joint line tenderness and 15m walking time in seconds were noted. The patients were reviewed at the end of 30th day, 90th day and 180th day and the same parameters were assessed. Patients were instructed to report immediately in the presence of any untoward effect.

Analysis of data

The data was coded and entered in MS Excel worksheet. Analysis was done using SPSS package. Qualitative data was summarized using frequency and percentage. Quantitative data was summarized using median and interquartile range (IQR). Association between qualitative data was analysed using Chi-square test and association between Quantitative data was done using independent sample t test. Baseline values and post - treatment values of overall pain using VAS, joint line tenderness and 15m walking time in seconds in each group were compared using Wilcoxon sign test. Comparison between the same parameters of the two groups was done using Mann Whitney U test. Significance level was fixed at a p value <0.05.

RESULTS

Thirty patients with osteoarthritis of the knee were evaluated in the descriptive comparative study, comparing the efficacy of intra articular hyaluronic acid with intra articular triamcinolone hexacetonide. All the patients in both groups completed the study. Table 1 shows the baseline parameters and was comparable in both groups.

Table 2 compares the efficacy of Hyaluronic acid over months using VAS for overall pain, joint line tenderness, 15m walking time in seconds. The values were expressed as the median and IQR of the differences of parameters between baseline and first visit (30 day) and base line and

third visit (180 day). There was a significant improvement in all parameters between the baseline and 30thday, baseline and 180th day post treatment values as revealed by Wilcoxon sign test. The improvement was more on 180th day.

Table 1: Comparison of baseline parameters.

Variable	Hyaluronic acid	Triamcinolone Hexacetonide	Test	P value
No. of males /females included	5/15(33.33%)	2/15(13.33%)	Chi square test	0.31
Mean age in years(X±SD)	53±2.7	52±4.6	Independent sample t test	0.06
Mean duration of osteoarthritis in years (X±SD)	3.3±2.3	3.4±1.6	Independent sample t test	0.24

Table 2: Comparison of efficacy of hyaluronic acid over months using different scales.

Variable	Difference between BL and 1st visit median (IQR)	P Value	Difference between BL and final visit median (IQR)	P Value
Over all pain VAS	1.47(1.41)	0.01	4.13(2.07)	0.001
Joint line tenderness	0.87(0.35)	0.01	1.73(0.45)	0.001
15m walking (performance based)	8.67(7.43)	0.002	10(7.56)	0.004

Table 3: Comparison of efficacy of triamcinolone hexacetonide over months using different scales.

Variables	Difference between BL and 1st visit median (IQR)	P value	Difference between BL and final visit median (IQR)	P Value
Overall pain VAS	4.33(1.40)	0.002	0.13(0.35)	0.84
Joint line tenderness	1.93(0.26)	0.01	0±0	0.76
15m walking time	17.3(7.76)	0.001	1.66(2.44)	0.14

Table 4: Comparison of efficacy between hyaluronic acid and triamcinolone hexacetonide using VAS for overall pain, joint line tenderness and 15m walking time at first visit.

Variables	Difference between base line and 1st visit hyaluronic acid median (IQR)	Difference between base line and 1st visit triamcinolone hexacetonide median (IQR)	P value
Overall pain using VAS	1.47(1.41)	4.33(1.40)	0.001
Joint line tenderness	0.87(0.35)	1.93(0.26)	0.01
15m walking time (sec)	8.67(7.43)	17.3(7.76)	0.002

Table 5: Comparison of efficacy between HA and THA using VAS for overall pain, joint line tenderness and 15m walking time at final visit.

Variable	Difference between base line and final visit hyaluronic acid median (IQR)	Difference between base line and final visit triamcinolone hexacetonide median (IQR)	P Value
Overall pain VAS	4.13(2.07)	0.13(0.35)	0.001
Joint line tenderness	1.73(0.45)	0±0	0.04
15m walking time	10(7.56)	1.66(2.44)	0.002

Table 3 compares the efficacy of triamcinolone hexacetonide over months by assessing VAS for overall pain, joint line tenderness, 15m walking time in seconds. The values were expressed as median and IQR of the difference between baseline and first visit and baseline and third visit values. There was highly significant improvement in all the parameters on the 30th day of treatment. However, the improvement was not seen at the end of 6 months. Many of the parameters didn't show any improvement or worsened at the end of 6 months. Table 4 compares the efficacy of hyaluronic acid with triamcinolone hexacetonide with reference to VAS for

overall pain, joint line tenderness and 15m walking time in seconds on the 30th day of treatment. Values were expressed as median and IQR of the difference between baseline and first visit. The difference between the differences was compared using Mann Whitney U test. There was significant improvement in all parameters in favour of triamcinolone hexacetonide treated group.

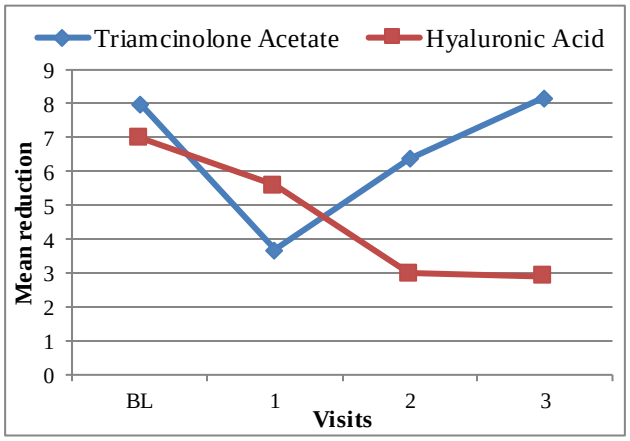

Figure 1: Mean reduction in overall pain using visual Analog scale with two regimens.

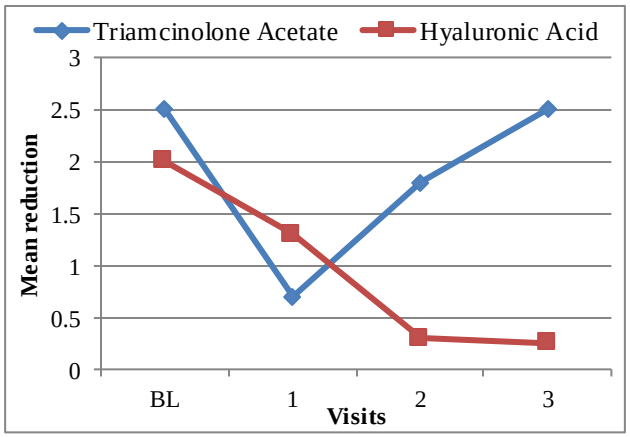

Figure 2: Mean reduction in joint line tenderness with two regimens.

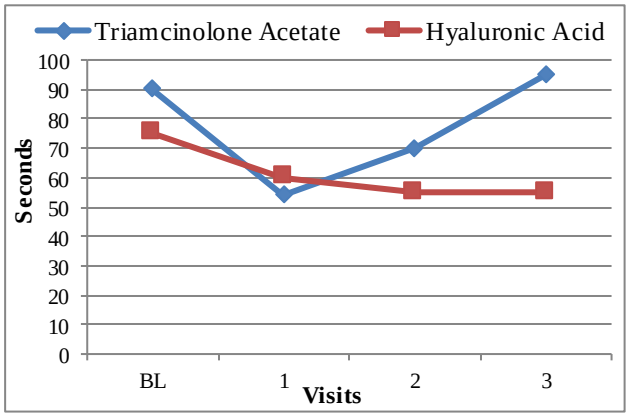

Figure 3: Improvement in 15m performance based walking.

Table 5 compares the efficacy of hyaluronic acid with triamcinolone hexacetonide with reference to the above parameters on the 180th day of treatment. Improvement was more for HA Group in all parameters compared to THA group and the difference between the differences was highly significant clinically and statistically.

Figures 1, 2 and 3 compare the efficacy of HA and THA using various parameters. All parameters showed a significant improvement in case of THA as compared to HA at the end of 1st month. However, at the end of 6 months all the parameters showed deterioration in THA group. Even though the improvement was slow in case of HA group, the improvement was long-lasting.

DISCUSSION

The present study was a descriptive comparative study to compare the efficacy and safety of intra articular hyaluronic acid and intra articular triamcinolone hexacetonide in 30 patients with primary osteoarthritis knee. The efficacy assessment of hyaluronic acid using VAS for overall pain, joint line tenderness and 15m walking time in seconds for pain disability and functional impairment showed a significant reduction from 30th day onwards. This result was comparable to result of a study by Brandt et al on 226 patients with osteoarthritis knee to evaluate the efficacy of intra articular injections of sodium hyaluronate. Patients were randomized to 3 weekly injections of sodium hyaluronate or physiologic saline and observed for additional 25 weeks. WOMAC Score, patient and investigator global assessments and pain on standing showed significant improvement from week 7 through 27 weeks in sodium hyaluronate group.[19] In a prospective study conducted by Chandra Praash Pal, et al to evaluate the effect of intra articular Hyaluronic acid in 112 patients who were randomised to weekly injections of HA or normal saline and observed for 36 weeks significant reduction in weight bearing pain, resting pain VAS and WOMAC Scores were noted from 12 weeks onwards.[20]

The proposed mechanism of action of HA activity occurs in two stages-a mechanical stage and a pharmacological stage.[21,22] OA synovial fluid is replaced by higher concentrations of HA there by improving viscosity in mechanical stage.[23] This also restores the shock absorbing and lubricating abilities of depleted synovial fluid and maintains a boundary layer around nociceptors reducing pain induction.[24] The pharmacological stage induces the synthesis of endogenous HA and extracellular matrix components, which reduces proteoglycan loss in cartilage and apoptosis of chondrocytes.[25] Also it reduces the inflammatory cell activities to reduce HA degradation and acts by reducing induction of pain mediators.[23,24]

On assessing the efficacy of triamcinolone hexacetonide using VAS for overall pain, tenderness index and 15m walking time in seconds showed significant improvement at the 30th day. However, this improvement was not seen at the end of 6months. Our result was comparable to the

study done by UmutYavuz et al, on 120 patients with osteoarthritis knee comparing the efficacy of three corticosteroid injections with placebo.[26]

Corticosteroids exert their anti-inflammatory action by interrupting the inflammatory and immune cascade at several levels including impairment of antigen opsonisation, interference with inflammatory cell adhesion and migration through vascular endothelium, impairment of leukotriene and prostaglandin synthesis, inhibition of production of neutrophil superoxide, metalloprotease, metalloprotease activator and decreased immunoglobulin synthesis.[27]

Earlier studies have reported that corticosteroids injections may suppress cartilage proteoglycan synthesis or even cause degenerative lesions in cartilage.[28] On the other hand, using animal model several investigators have reported that low dose intra-articular corticosteroids normalised cartilage proteoglycan synthesis and also it significantly reduced the incidence and severity of cartilage erosions and osteophyte formation.[29]

On comparing the efficacy of hyaluronic acid with triamcinolone hexacetonide, at 30 days, revealed a significant improvement in all parameters in favour of THA. During the next 5 months follow up period, significant improvement in all parameters in favour of hyaluronic acid treated group was noted. The result was comparable to a randomised multicentre single blind comparison of hylanG-F20 [n=113] and intra articular triamcinolone hexacetonide [n=102] for primary osteoarthritis knee. Primary assessments were WOMAC question A1 and a 100mm VAS for patient and investigator overall assessment. Maximum pain relief occurred at 1-2 weeks for THA, and at weeks 12 and 26 Hylan GF20 was significantly better than THA.[30] No clinically significant local or systemic adverse effects were noted in both the treatment groups. Both treatments were well tolerated.

This study concluded that intra articular triamcinolone hexacetonide has superior short-term efficacy compared to hyaluronic acid but in the long term, hyaluronic acid has superior effect. The only limiting factor is its high cost. Osteoarthritis being a chronic disease process, we need a drug which has a long-lasting effect. Additive effect of hyaluronic acid and triamcinolone hexacetonide can be considered for better efficacy.

CONCLUSION

This clinical study was undertaken to compare the efficacy and safety of recommended doses of intra articular Hyaluronic acid and intra articular Triamcinolone hexacetonide in 30 patients, 15 being in each group. The efficacy was measured with various parameters for a period of 6 months.

The study has shown that triamcinolone hexacetonide has superior short- term efficacy whereas hyaluronic acid has long lasting effect. Both treatments were well tolerated by the patients. Injection with corticosteroids or HA are used for the treatment of knee osteoarthritis when oral therapy does not provide adequate symptom control. Drawback of HA is multiple weekly injections over 3-5 weeks and also high cost. The use of HA in combination with THA appears to give a rapid onset of symptom relief with increased duration of response and no apparent increase in toxicity. Additional research has to be done to better define the role of this combination. Also, future studies should be conducted to examine if HA preparations can provide equal efficacy with compressed dosing schedule compared to traditional multiweek dosing.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of GMC, Kozhikode

REFERENCES

1. Dhar HL. Common disease and elderly. Bombay Hospital Journal. 2002 Jan;44(1):61-7.
2. Hadler NM. Knee pain is the malady not osteoarthritis. Ann Intern Med. 1992;116(7);598-9.
3. Wehling P, Evans C, Wehling J, Maixner W. Effectiveness of intra-articular therapies in osteoarthritis: a literature review. Therapeutic Advances in Musculoskeletal Disease. 2017;9(8):183-96.
4. Lawrence RC, Felson DT, Helmic CG. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States Part II. Arthritis Rheum. 2008;58:26-35.
5. Brant D, Smith GN Jr, Simon LS. Intraarticular injection of hyaluronan as treatment for knee osteoarthritis-what is the evidence? Arthritis Rheum. 2000,43:1192-203.
6. Mandell BFF, LipaniJ. Refractory osteoarthritis. Differential diagnosis and therapy. Rheum Dis Clin North Am. 1995; 21:163-78.
7. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. The Journal of rheumatology. Supplement. 1993;39:3-9.
8. Grecomoro G, Piccione F, Letiza G. Therapeutic synergism between hyaluronic acid and dexamethasone in the intra-articular treatment of osteoarthritis of the knee: a preliminary open study. Curr Med Res Opin. 1992;13:49-55.
9. Leardini G, Mattara L, Franceschini M. Intra-articular treatment of knee osteoarthritis. A comparative study between hyaluronic acid and 6 methyl prednisolone acetate. Clin Exp Rhematol. 1991;9:375-81.
10. Pietrogrande V, Melanotte PL, Agnolo DB. Hyaluronic acid versus methylprednisolone intra articularly injected for the treatment of osteoarthritis of the knee. Curr Ther Res. 1991;50:691-70.

11. Guidolin DD, Ronchetti IP, Lini E. Morphological analysis of articular cartilage biopsies from a randomised clinical study compoaring the effects of 500-730Da sodium hyaluronate (Hyalgan) and methyl prednisolone acetate on primary osteoarthritis of the knee.Osteoarthritis Cartlage. 2001;9:371-81.
12. Adams ME, Atinson MH, Lussier AJ. The role of viscosupplementation with Hylan G-F20 (Synvisc in the treatment of osteoarthritis of the knee: a canadianmulticeenter trial comparing hylan G-F20 alone,hylan G-F20 with non-steroidal anti inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoartritis Cartilage. 1995;3:213-25.
13. Brandt KD, Block JA, Michalski. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. ClinorthopRelat Res. 2001;385:130-43.
14. Miltner O, Schneider U, Siebert CH. Efficacy of intraarticularhyaluronic acid in patients with osteoarthritis-a prospective clinical trial. Osteoarthritis and Cartilage. 2002;10(9):680-6.
15. Brocq O, Tran G, Breuil V. Hiposteoarthritis: short term efficacy and safety of visco supplementation by Hylan G-F20.An open-label study in 22 patients. Joint Bone Spine. 2002;69:388-91.
16. Maheu E. Hyaluronan in knee osteoarthritis. A review of the clinical trials with Hyalgan. Eur J RhematolInflamm. 1995;15:17-24.
17. Henderson EB, Smit EC, Pegley F. Intra-articular injections of 750D hyaluronan in the treatment of osteoarthritis.A randomised single center double blind placebo- controlled trial of 91 patients demonstrating lack of efficacy.Ann Rheum Diss. 1995;53:529-34.
18. Berenbaum F, Grifka J, Cazzaniga S, D'amato M, Giacovelli G, Chevalier X, et al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Annals of the rheumatic diseases. 2012;71(9):1454-60.
19. Brandt, Kenneth D. Bloc, Joel A, Michaelsi, Joseph P. Clinical Orthopedics & Related Research. 2001;385;130-143.
20. Pal CP, Sadana A, Goyal A. Therapeutic efficacy of intraarticular Hyaluronic acid in osteoarthritis knee JBJD. 2017;32(1):44-9.
21. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum. 2009;61:1704-17.
22. Bagga H, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol. 2006;33:946-50.
23. Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: Are the effects molecular weight dependent? Seminar Arthritis Rheum. 2002;32:10-37.
24. Pozo MA, Balazs EA, Belmonte C. Reduction of sensory responses to passive movements of inflamed knee joints by hylan, a hyaluronan derivative. Exp Brain Res. 1997;116:3-9.
25. Diaz-Gallego L, Priweto JG, Coronel P. Apoptosis and Nitric oxide in an experimental model of osteoarthritis in rabbit after hyaluronic acid treatment. J Orthop Res. 2005;23:1370-6.
26. Yavuz U, Sami S, Albayraketal A. Efficacy comparisons of the intraarticular steroid agents in the patients with knee osteoarthritis. Rheumatology International. 2012;32(11):3391-6.
27. Wilder RL. Corticosteroids. In: lippel JH, Cornelia WM, Wortmann RL, eds. Primer on the rheumatic diseases. Atlanta: Arthritis Foundation.1997;427-31.
28. Pelletier JP, Haraoui B, Martel-Pelletier J. Modulation of cartilage degradation in arthritic diseases by therapeutic agents. Inflammatory disease and therapy. 1993;12:503.
29. Pelletier JP, Martel-Pelletier J. Protective effects of corticosteroids on cartilage lesions and osteophyte formation in the pond-nuki dog model of osteoarthritis. Arthritis and Rheumatology. 1989;32(2):181-93.
30. Caborn D, Rush J, Lanzeretal W. A randomised single blind comparison of the efficacy and tolerability of hylanG-F20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. The J of Rheu. 2004;31(2):333-43.

Cite this article as: Kizhedath S, Valoth G, Vasudevan B. Intra articular hyaluronic acid versus intra articular triamcinolone hexacetonide in primary osteoarthritis of knee: a comparative study. Int J Basic Clin Pharmacol 2017;6:2794-9.