Efficacy of radiosynovectomy in the treatment of chronic knee synovitis: Systematic review and meta-analysis

Systematic Review

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ABSTRACT

Introduction: Knee joints are commonly involved with various inflammatory and non- inflammatory rheumatic diseases. Radiosynovectomy is being used as a local therapeutic option to alleviate pain and swelling in involved joints. The present study evaluated the effectiveness of radiosynovectomy for treatment of chronic knee synovitis.

Methods: Through a search of Medline and SCOPUS with (Radiosynovectomy OR radio-synovectomy OR "radio synovectomy" OR "radiation synovectomy" OR radiosynoviorthesis OR radio-synoviorthesis OR synoviorthesis OR "radiochemical synovectomy" OR "radioisotope synovectomy") AND (Re-188 OR Y-90 OR Sm-153 OR P-32) as key words, 9 RCTs were enrolled in the analysis.

Results: The outcomes of interest were odds ratio and risk difference of improvement in the radiosynovectomy group compared to the control group. Odds ratio and risk difference for Sm-153 plus corticosteroid subgroup was 1.959[0.571-6.725, P=0.285] and 14.9% [-17.1%-47%, P=0.362] respectively. The subgroup of Y-90 plus corticosteroids showed pooled odds ratio and risk difference of 2.366[0.779-7.188, P=0.129] and 23.9% [-1.7%-49.4%, P=0.67] and in the subgroup Y-90 alone were 0.851[0.356-2.036, P=0.717] and -2.3% [-23.3%-18.7%, P=0.829], respectively.

Conclusion: Combination of Y-90 colloid or Sm-153 with corticosteroids in radiosynovectomy have higher response rate compared to each of radioisotope or corticosteroid therapy alone.

Key words: Synovectomy; Arthritis; Radionuclide; meta-analysis

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INTRODUCTION

Inflammatory and non-inflammatory chronic synovitis of knee joints is a common cause of joint deformity. Chemical, radio isotopic and surgical synovectomy are being used as therapeutic options for chronic synovitis in order to improve joint function [1].

Triamcinolone Hexacetonide (TH) and osmic acid are the most frequent agents which have been used as chemical synovectomy. Controlled studies showed that TH has the least solubility, longest duration in the articular space and utmost effectiveness among corticosteroids for local treatment. However, it causes temporarily pain relief and frequent intra articular injections are not recommended [2]. Intra articular injection of Osmic acid is a painful procedure with variable results [3]. Surgical synovectomy through arthroscopy or open techniques has success rate of 40-90%. Prolonged rehabilitation results in joint stiffness and its outcome is dependent on the amount of joint damage [4, 5].

Radio isotopic synovectomy also known as radiation synovectomy, radiosynovectomy or radiosynoviorthesis (RSO) is another local treatment procedure using injection of radioactive isotope in colloid form with appropriate physical characteristic into the joint capsule [6]. RSO first was applied as a local form of radiotherapy by Fellinger et al. in 1952 and has been used for decades to alleviate pain and swelling in involved joints [7, 8]. Knee joints are commonly involved in rheumatoid diseases with considerable morbidity for the patients. Although radiosynovectomy is considered as an effective method for treatment of chronic knee synovitis, few randomised controlled trials have evaluated the efficacy of this type of treatment for chronic knee synovitis with various (and sometimes contradictory) results.

In the current study, we searched the available medical literature regarding the efficacy of radiosynovectomy for chronic knee synovitis and reported the results in systematic review and meta-analysis format. Thus far, four systematic reviews have been published in the literature [9-12].

None of these systematic reviews evaluated the knee joint specifically. In addition, they included all available studies not the best available procedures (which are RCTs).

The last meta-analysis by Var de Zant et al has included studies before 2007 and in our opinion another systematic review is needed. So the aim of the study is to evaluate the clinical question of efficacy of radiosynovectomy in chronic knee joint synovitis by including only the RCTs.

METHODS

Search strategy

We performed a comprehensive literature review in the MEDLINE and SCOPUS data bases using the following keywords: (Radiosynovectomy OR radio-synovectomy OR "radio synovectomy" OR "radiation synovectomy" OR radiosynoviorthesis OR radio-synoviorthesis OR synoviorthesis OR "radiochemical synovectomy" OR "radioisotope synovectomy") AND (Re-188 OR Y-90 OR Sm-153 OR P-32).

Study selection

The search was done by two authors independently. Criteria for the inclusion were all RCTs evaluating the efficacy of radiosynovectomy with appropriate radiotracers ((Re-188, Y-90, Sm-153, or P32) in the knee. The final decision was based on the full article. Duplicated papers were excluded. No language or date limit was applied on the search.

Quality evaluation

For scoring, the quality of included articles and the Oxford Centre of Evidenced-based Medicine levels of Evidence for therapy studies (http://www.cebm.net/index.aspx?o=5653) were used for evaluation of quality of studies.

Data extraction and analysis

Data of each included study on patients' characteristics, randomization, treatment and control protocols, treatment effect and lost to follow up are retrieved by two authors independently. Odds ratio and risk difference of improvement in the radiosynovectomy group compared to the control group were used as the outcomes of interest. Random effects model (Dersimonian and Laird method) was used for pooling the data. Cochrane Q test was used for evaluation of heterogeneity across the studies. P-value less than 0.05 were considered statistically significant. I^2 index was used to quantify the amount of heterogeneity across the included studies. All statistical analyses were done using Comprehensive Meta-Analysis Ver.2.

RESULTS

169 potential studies were identified at the initial search**.** Review of the titles and abstracts excluded 108 studies. The full texts of the remaining 61 articles were evaluated in depth leading to exclusion of 49 studies in this step.

Table 1: The characteristics of the included studies as well as their quality assessment.

Author	Years of publication	Number of knees	Radioisotope	Randomization	Similarity between two groups	Objective and double blind assessment of outcome	Compare to
Bridgman	1973	44	Y-90	yes	yes	Yes	Saline
Gumpel	1975	21	Y-90	yes	yes	N/A	SS
Nissilä	1978	66	Y-90	yes	yes	N/A	SS/OA
Sheppeard	1981	175	Y-90	yes	yes	yes	OA
Doherty	1981	30	Y-90+TH	yes	yes	yes	Saline+TH
Grant	1992	30	Y-90	yes	yes	yes	TH
O'Duffy	1999	31	Sm-153+TH	yes	yes	yes	TH
Zalima	2005	101	Y-90+TH	yes	yes	yes	Saline+TH
Dos Santos	2011	87	Y-90/Sm-153+TH	yes	yes	yes	TH

TH: Triamcinolone hexacetonide; SS: Surgical synovectomy; OA: Osmic acid

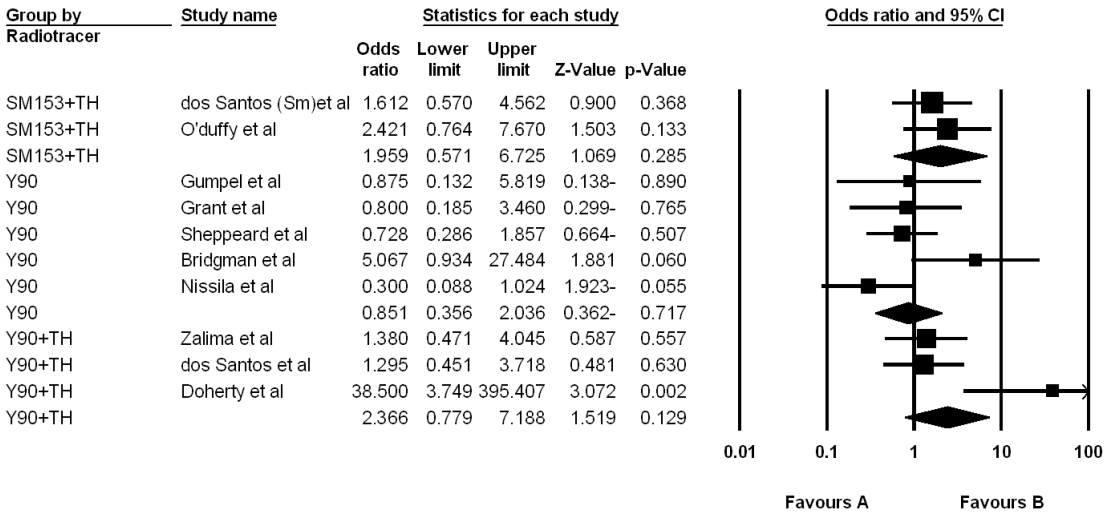

Fig 1. Forest plot of odds ratio with 95% confidence intervals.

Overall 9 RCTs were included in the systematic review with 308 knee joints in treatment group and 306 as control group for comparison [13-21]. One study (dos Santos et al) evaluated the efficacy of Sm-153 and Y-90 separately. Each part is evaluated separately in our analysis. No RCT was found for P-32 or Re-188. Two studies used Sm-153 and 8 studies used Y90. Table 1 shows the characteristics of the included studies as well as their quality assessment.

Figures 1 and 2 show the forest plot of odds ratio and risk difference pooling across studies. Two studies used Sm-153 in addition to Intra-articular corticosteroid and compared to the control group showed pooled odds ratio and risk difference of 1.959 [0.571-6.725, P=0.285] and 14.9% [-17.1%-47%, P=0.362], respectively meaning that the odds of improvement in the treatment group (Sm-153+corticosteroid) is 1.959 times more than the control group and the treatment group (Sm-153+corticosteroid) has 14.9% more chance of improvement compared to the control group. Among the Y-90 studies, two subgroups could be identified: 5 studies used Y-90 alone and 3 studies used Y-90 plus corticosteroid as the treatment arms. The subgroup of Y-90 only, showed pooled odds ratio and risk difference of 0.851[0.356-2.036, P=0.717] and -2.3% [-23.3%-18.7%, P=0.829] respectively. The subgroup of Y-90 plus corticosteroids showed pooled odds ratio and risk difference of 2.366[0.779-7.188, P=0.129] and 23.9% [-1.7%-49.4%, P=0.67] respectively. Cochrane Q values and I^2 indices for the subgroups of Sm-153 plus TH, Y-90 alone and Y-90

plus TH were 0.263 (0%), 7.068(43.4%) and 7.248 (72.4%) respectively. There is no consensus validated system to measure outcome of the clinical effect of radiosynovectomy. Majority of studies have been used subjective and objective scoring system for the effect of the therapy. Intra articular corticoid injection, surgical synovectomy and changes in systemic therapies are applied in unresponsiveness patients to RSO.

DISCUSSION

Radiosynovectomy is being used for a long time as a therapeutic intervention for synovitis. Beta emitting radioisotopes attached to the colloids are phagocytized by the macrophages applying the radiation effect on the inflamed layer of synovial membrane [6]. The main purpose of RSO is to destroy the pannus and inflamed synovium by direct radiation. The penetration depth of radio colloid should relate to the thickness of the synovial membrane. The type of radio colloids which are suitable for RSO is determined by the size of the joint. The higher range Beta rays are used for knee joints. [22] For treatment purpose approximately 100Gy per 100g of synovial tissue should be absorbed to have an optimal effect and the recommended limit for the total dose per session is 400 Mbq [23]. A large number of radionuclides have been used for radiosynovectomy in patients suffering from knee joint pathology. Au-198 colloid, P-32 colloid and Dy-165 ferric hydroxide are being used in the United States. They are not recommended in EANM guideline any longer owing to adverse effects such as high lymphatic transport [24]. The characteristic of radiopharmaceuticals, which are being used in the present meta-analysis, are shown in Table 2. Y-90 is the most popular radioisotope used for the treatment of chronic knee synovitis.

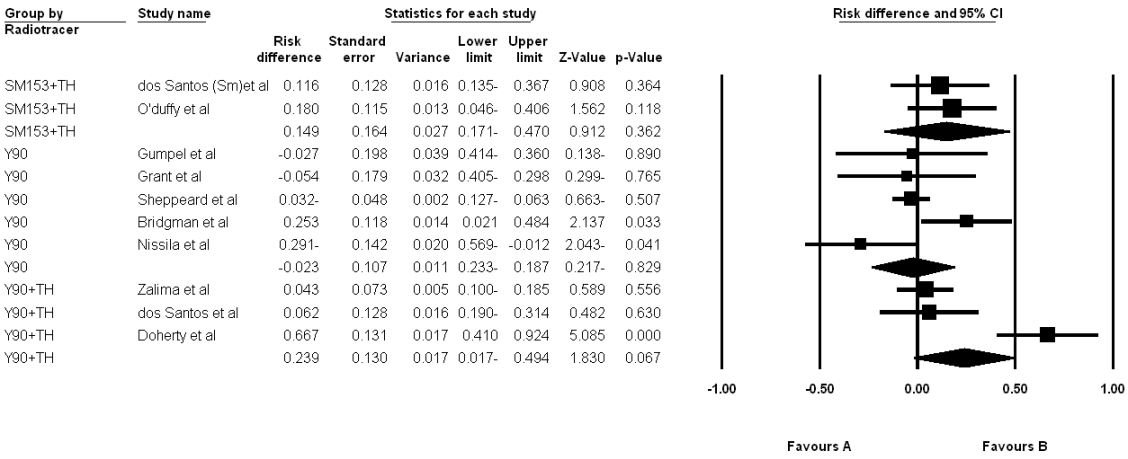

Fig 2. Forest plot of risk difference with 95% confidence intervals.

Table 2. The characteristic of radiopharmaceuticals used for radiation synovectomy.

	Re-188 colloid	Y-90 silicate-citrate colloid	Sm-153 particulate hydroxyapatite
Physical half-life (h)	16.9	64.1	46.3
Maximum beta energy (MeV)	2.12	2.26	0.29
Gamma energy (keV)	155	-	103
Mean particle size (nm)	500-1000	100	1600-2200
Tissue range (mm)	5-10	3.6-11	0.7-3.1
Recommended activity (MBq)	555-925	185	555

Sm-153 particulate hydroxyapatite and Re-188 colloid relatively new agents and were also used. There are few studies based on randomized clinical trial for evaluation of the effectiveness of RSO. There are no consensus methods for study design, using radioisotope with or without intra articular corticosteroid. In addition, one of the major limitations is inadequate number of RCT studies based on using Sm-153 particulate hydroxyapatite and Re-188 colloid for knee synovitis. In present meta-analysis 9 randomized clinical trials were included. Depending on the radioisotope used, we compared these studies in three different groups. Pooled odds ratio in Y-90 colloid versus TH is 0.851 indicating the result of RSO with Y-90 alone is less effective than intra articular corticosteroid. Although pooled odds ratio favouring RSO with Y-90 plus TH is 2.36 compared to TH alone, the exact mechanism of this finding is not clear. We suggested that because clinical parameter such as pain, range of motion and joint effusion are main factors for evaluation of the success rate. Down regulation of pro-inflammatory proteins are the possible mechanism for intra articular corticoid injection and temporarily reduction of pain and inflammation in the affected joints [25]. Combination of Y-90 colloid and TH has synergistic effect in improvement of patient's symptoms. Pooled odds ratio for RSO of the knee with Sm-153+TH versus TH is 1.959. However, only 3 studies compared Sm-153 plus TH versus TH. More studies are needed for valid conclusion. It has been evident from forest plot that the concomitant use of Sm-153+TH is more effective than TH alone.

CONCLUSION

Combination of Y-90 colloid or Sm-153 with corticosteroids in radiosynovectomy have higher response rate compared to each of radioisotope or corticosteroid therapy alone.

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