Management of chronic synovitis in patients with hemophilia: with special reference to developing countries

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Abstract Chronic synovitis in severe hemophilia is a painful debilitating condition eventually affecting greater than 20% severe hemophilia patients in developing countries. Though this complication is all but eliminated in the countries with advanced hemophilia care and having access to generous factor concentrate replacement, the same can not be said for 80% of the hemophilia patients in the world who live in developing countries. In developing countries chronic synovitis can be treated conservatively with short course of steroid, factor replacement, physiotherapy and splintage. Failing this, chemical or radioactive synoviorthesis give worthwhile remission and relief in 70–80% of the severely affected patients who fail to respond to conservative therapy. We found a short course of Cox-2 (etoricoxib) inhibitor to be an extremely useful adjunct. The role of d-Pencillamine, Thalidomide and inhibitors of matrix metalloproteinases needs to be explored. HLA-B27 was found to be strongly associated with chronic synovitis in hemophilia in one of the studies and this marker in a hemophilia patient may suggest need for more intensive replacement and other therapy in these patients to prevent chronic synovitis.

Keywords Chronic synovitis · Developing countries · HLA-B27 · Radioactive synoviorthesis

Introduction

As hemophilia care has improved steadily in the western countries from therapy with Fresh Frozen Plasma (FFP), cryoprecipitate, plasma derived factor concentrates to recombinant factor concentrates, many of the complications of severe hemophilia which were seen in 1970 and even in 1980 have become a thing of the past.

Unfortunately however, the same thing can not be said about the hemophilia patients in large part of developing world where 80% of the world hemophilia patients reside. In developing countries, the priorities of health care lay in controlling infectious diseases, providing safe water, controlling nutritional deficiencies rather than spending meagre resources on high cost low volume hemophilia care. Factor concentrates for hemophilia care still needs to be imported by spending precious and hard earned foreign currency. Hence, there has always been a need to develop treatment modalities to treat some of the chronic complications of hemophilia suitable for developing countries. Chronic synovitis is one such complication and the following write-up describes some of the developments, which may be suitably incorporated in the management of chronic hemophilic synovitis in developing countries.

Pathophysiology of chronic synovitis in hemophilia

Repeated joint bleed is involved in the pathogenesis of chronic synovitis. When joint bleed is indeed experimentally repeated in rabbit's chronic synovitis results. Pathologically the joint gets swollen, inflamed with synovial cells staining, with haemosiderin obtained from degraded haemosiderin. Similar pathology has been noticed when hyper

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trophic synovium removed from chronic synovitis patients were examined microscopically [1]. It is believed that reactive oxygen species, hemoglobin, matrix metalloproteinases released from neutrophils and macrophages continues this damage. If the bleeding is recurrent then the joint does not get enough time for full recovery leading to chronically inflamed, swollen and boggy synovium of chronic synovitis (Fig. 1).

However, even after recurrent bleed every patient with severe hemophilia does not get through a phase of chronic synovitis. Though eventually a large majority of such patients develop chronic hemophilic arthritis, a form of degenerative arthritis, only 20% of such patients go through a phase of chronic synovitis [2]. Our study showed that HLA-B27 is strongly associated with the development of chronic synovitis [2, 3]. This information may be of some use in managing these patients by more intensive prophylaxis and physical therapy.

Management of chronic synovitis in severe hemophilia

Best form of management of chronic synovitis in severe hemophilia is to prevent it by regular replacement of factor VIII or factor IX prophylactically till the child grows upto 18–20 years of age [4]. In the developing countries and in a large part of the developed world the primary prophylaxis is too costly to be adopted as a primary form of treatment. Hence, the management of established chronic synovitis can be considered under following heads.

The treatment of choice for established chronic synovitis is a fairly long term programme of regular factor replacement (3 times a week for factor VIII and twice a week for factor IX, for at least 3 months) aiming for 40–50% correction during each injection. This should be coupled with regular physical therapy to achieve compact muscular atrophy and to build up the muscles around affected joints if the muscles have already undergone atrophy. Improvement of muscle bulk is often slow, hence patience is required and persistence with exercise is always rewarded. If this scheme of management fails then the patient should undergo open or better arthroscopic synovectomy following factor replacement [5, 6].

In our comprehensive hemophilia care centre we manage chronic synovitis as follows.

- (i) A short course of oral Prednisolone (10 mg once daily) after breakfast for 7 days.
- (ii) 4–5 injections of factor concentrates given on alternative days.
- (iii) Physiotherapy with a view to prevent muscular atrophy, sufficient muscular balance of the joint

Fig. 1 Showing a florid chronic synovitis in a patient with severe haemophilia, scar marks show previous attempts at joint aspiration elsewhere

and improvement of co – ordination and proprioception [7].

- (iv) In selected cases ultrasound application to the joint significantly expedited the recovery.

In Frankfurt, Germany [8] since 1981, 158 adults and 61 children were treated with interdisciplinary approach. It was found that soft heal shock absorber, elastic and semi rigid bandages prevented recurrent bleeding episodes by shock absorption and decrease in synovial impingement. Radiosynoviorthesis was required in 12 of their cases.

In certain patients though synovitis is reduced by intense conservative approach, a given amount of flexion deformity remained and this was corrected at our centre with dual force traction [9], in western countries more costly flowtron system [10] can be used. Chronic synovitis of hemophilia has also been treated with some success with Cox-2 inhibitors [11] intra articular methyl prednisolone [12] and, d-penicillamine [13, 14]. We found combining sequentially or concurrently a short course of prednisolone with Cox-2 inhibitor (Vioxx – 25 mg /day or etoricoxib

60 mg/day for an adult) was extremely useful. Unfortunately Vioxx was withdrawn from the market for its effect on coronary artery disease, when used for a long time but we have never used this medicine longer than 7–10 days at a stretch and we have used it on 600 severe hemophilia patients over last 4 years, some times in repeated courses of 7 days each without any reported problem. Of course, our hemophilia patients are mostly under 20 years of age and additional coagulation defect could have been protective in these patients against atherthrombotic complications.

After trying conservative treatment, a proportion of patients fail to respond. These patients need more aggressive treatment such as open arthroscopic synovectomy, arthrodesis, joint replacement. Now a days, arthroscopic synovectomy is preferred to open synovectomy and joint replacement gives a better range of movement. Both arthrodesis and joint replacement stops recurrent bleeding from the joint [15].

However, both arthroscopic synovectomy and joint replacement are costly procedures. Apart from the costs of operation and prosthesis, the cost of prolonged factor replacement needed with these procedures increases the cost of the procedure 4–10 times that of the same operation done on nonhemophilic patients.

Hence, cheaper alternatives like chemical synoviorthesis by injecting Rifampicin in the joint is gaining popularity [11, 16]. Chemical synoviorthesis requires 6–8 injections given in the affected joint after single injection of factor replacement and the joint is put under a compression bandage for 24–28 hours after which gentle passive movements are commenced. This procedure using Rifampicin was effective in 75% of our 26 patients treated in this way (unpublished observation). These patients are free of bleeding and pain for last 5 years; 3 patients with knee joint synovitis, 2 patients with recurrent synovitis of the shoulder joint and 2 patients with elbow joint had early recurrence or did not respond to this treatment. One of the centres in India, Pune, has successfully used radio synoviorthesis using yttrium 90 as the radio isotope with satisfactory results, several other reports also testify the effectiveness of this procedure [17]. In USA ^{32}P is the recommended isotope for this procedure [18]. All these isotopes are β emitting and have limited penetrating ability. These isotopes are used in colloidal form so that the material remains in the joint and the systemic absorption from the joint is low.

Radioactive synoviorthesis has an additional advantage over chemical synoviorthesis in requiring only one dose of factor concentrate and one sitting of intrasynovial injection. Radioactive yttrium is costly but this cost is offset by the requirement of single factor concentrate injection in lieu of 6–8 for chemical synoviorthesis. Radioactive phospho-

rous is not costly and also requires one injection of factor concentrate. However, we have observed that injection of radioisotopes needs special permission facilities and license which chemical synoviorthesis does not require and still cheaper and widely available tetracycline can be used in lieu of rifampicin injection with similar results.

Discussion and conclusion

Chronic synovitis still affects greater than 20% of the severe hemophilia population in the developing world. Conservative management with factor replacement therapy, graded physiotherapy and initial splintage of joint improves the condition in majority of the patients. Dual force traction can correct flexion deformity. Light weight splintages using thermoplastic material, crepe bandages or still cheaper aluminum sheet with proper padding have helped many patients at our comprehensive hemophilia care centre. Ultrasound can be used judiciously to reduce pain and release soft tissue contractures. Low dose steroid, Cox-2 inhibitors, have been used with substantial benefit in these patients. Penicillamine as a therapy for chronic synovitis needs further assessment. Whether any of the above mentioned modalities of treatment is of definite benefit has not been studied in randomized clinical trials and it is unlikely that such trials will be done in developed countries. However, in countries where factor concentrate is still not available and primary prophylaxis with factor concentrates is still a distant dream such trial needs to be conducted. In our clinical experience, we have found the above mentioned therapies including short course of corticosteroids quite helpful in selected cases of chronic synovitis in shortening the period of synovitis and reducing the requirement of factor concentrates. Matrix metalloproteinase is considered to be one of the important tissue damaging enzymes released from neutrophils in the joints of chronic synovitis due to recurrent hemorrhage. Specific inhibitors for this enzyme may have a role in reducing the joint inflammation in these patients. Chemical and radioactive synoviorthesis was found to be safe, cheap and gave long lasting relief to most of our real chronic synovitis patients and this technique needs to be used more extensively.

Finally, those patients who do not respond to any of these approaches may be treated by open synovectomy followed by joint replacement or rarely with arthrodesis. We must not forget that there are many similarities in joint inflammation in chronic synovitis in hemophilia with that of chronic synovitis found in rheumatoid arthritis or ankylosing spondylitis and in the beginning of chronic synovitis in hemophilia patients these proliferation with the

vascular proliferative synovium. Hence, simple angiogenesis inhibitor like thalidomide may have a place in management of this complication in hemophilia and the additional thrombophilia property of this drug may be beneficial in hemophiliacs. In future intra articular injection of vascular endothelial growth factor (VEGF) inhibitors or antibodies may produce similar effect. It was sad that Cox-2 inhibitor “Vioxx” was withdrawn from the market, it is possible that this medicine, as an additional option would have had some use in pain relief for patients with bleeding disorders, even in western countries. We cannot use many anti inflammatory medicine for hemophilia patients due to their ability to interfere with platelet function. When we consider analgesia due to various joint and musculoskeletal bleeds in hemophilia patients, there are few medicines like paracetamol, opiates or various combinations of it to consider. Vioxx (Rofecoxib), celecoxib and etoricoxib was found to be a good anti-inflammatory drug for pain relief and reduction of inflammation of chronic synovitis in hemophilia patients without increasing bleeding tendency. We have used it in 600 hemophilia patients (never more than 7–10 days at a stretch), with no bleeding, good pain relief and with good effect on chronic synovitis.

Finally as HLA-B27 [3] was found to be strongly associated with this complication of hemophilia, a preventive approach to this condition may be more intense replacement therapy in those hemophiliacs who are positive for HLA-B27. Chronic synovitis in a hemophilic is a painful debilitating condition; this needs a team approach with hematologist, occupational therapist/physiotherapist, orthopedic surgeon, counsellor and anesthetist for optimum recovery and analgesia.

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