Radiosynoviorthesis in children with haemophilia

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Summary
Recurrent bleeding into joints represents the clinical hallmark of haemophilia and, if not adequately treated, it may cause chronic synovitis and degenerative arthropathy. The first treatment option of recurrent haemarthroses and/or chronic synovitis is represented by synoviorthesis, both chemical and radioisotopic, with a success rate of approximately 80% for both. However, radioisotopic synoviorthesis should be preferred because it makes it possible to obtain complete synovial fibrosis usually in one session, without the need for repeated injections, thus reducing the risk of bleeding complications and concentrate consumption. For all these reasons this procedure should be implemented and supported, particularly in developing countries.

Data and discussion
From 1971 several series reported the results of radioactive synoviorthesis (RS) in haemophilia patients similar to those of surgical synovectomy, with approximately 80% success with significant (>50%) bleeding reduction (1, 4, 6, 10, 14, 16), also after a long-term follow-up (6). Moreover, the rigorous physical therapy and factor infusion regimen, that is crucial to achieve a favourable outcome after a surgical synovectomy, are not needed in this setting.

The selection of optimal radionuclide and dose is controversial. Gold (198Au), yttrium (90Y), phosphorus (32P), rhenium (186Re) and erbium (169Er) have been used to treat haemophilic synovitis (1, 4, 6, 10, 14, 16). The properties of these radioisotopes used in haemophilic patients are shown in Table 1. The selection of the radioisotope should take into account:
- physical properties: half-life, size of the radiocolloid, soft tissue penetration and
- clinical features: joint size, amount of joint fluid, synovial thickness.

The material should also be a pure beta-emitters, thereby minimizing the whole body exposure to gamma radiation. Therefore, 198Au should not be used because of gamma radiation emission and its small size. The safety of RS still remains a cause for concern. Although several chromosomal studies demonstrated the possibility of transitory damage without malignant transformation (4, 7), two cases of acute lymphocytic leukaemia related to RS were recently reported in two children with haemophilia (5).

To our knowledge only one study clearly showed the results of RS in haemophilic children with inhibitors. Löfqvist et al. (10) reported the results of 13 instances of RS using 198Au in five patients with low titre inhibitor at the time of the procedure. All procedures were performed using FVIII/FIX at neutralizing doses. Five joints were classified as good, one as fair and 7 as poor with a median follow-up of 69 months (range: 18-182 months). The authors concluded that, although the results are poorer than those for patients without inhibitors, RS should be considered because of its ease of use and the definite decrease in joint bleeding frequency.
Patients and methods

Patient selection

Preferably, the procedure should be performed before the onset of radiological signs of chronic arthropathy, as in the grades I–II of the classification proposed by Fernandez-Palazzi (7), in patients older than two years. In grade 1 cases, RS should be considered as a preventive treatment if there were more than 2-3 episodes of haemarthrosis in six months. Exceptionally, RS is indicated in some early cases of grade III arthropathy. At the time of the injection, the presence of lesion and/or infection of the skin in the joint area or the presence of acute haemarthrosis has to be considered absolute contraindication.

Procedure

The procedure of RS is summarised in Table 2. If uncertainty exists on needle position, intraarticular positioning of the tip is confirmed by performing a fluoroscopic arthrogram. The needle is washed with anaesthetic and corticosteroid to prevent transfer of material and possible burn, just after injection of the radioisotope and before its removal. One to three intraarticular injections (repeated every 3 months) of radioisotope are usually sufficient. For European countries the recommended isotope for the knee is 198Au at a dose of 185 MBq. 186Rh is better for elbows (56–74 MBq) and ankles (74 MBq).

In the paediatric population, it is advisable to approximately halve the dosage used for the adults. Considering the concern that radioactive materials evoke, their high cost and limited supply, it would be preferable to schedule patients to receive RS in groups of 6-8 patients in the same session.

Haemostatic treatment

Non-inhibitor patients

Data do not exist concerning the minimum factor plasma level useful to ensure haemostasis during synoviorthesis. Nevertheless, it is advisable to reach and maintain factor levels above 50%. The preoperative bolus injection of FVIII or FIX is usually given 15–30 minutes prior to the procedure. Strict clinical monitoring is recommended in order to prevent late re-bleeding.

Inhibitor patients

High-dose FVIII/IX replacement therapy may be used in the presence of low-titre inhibitors. In these cases, factor pharmacokinetics should be tested before the procedure in order to adjust treatment doses and intervals. Bypassing agents, such as rFVIIa and activated prothrombin complex concentrate (aPCC), represent the first choice in patients with high-titre inhibitors. aPCC is usually administered by bolus injections at a dosage of 75–100 IU/kg.

The preoperative bolus injection is given 15-30 minutes prior to the procedure and the following bolus injections should be administered every 12–24 hours. A total daily dose of 200 IU/kg should not be exceeded and antifibrinolytic drugs never administered in association with bypassing agents. rFVIIa can be administered by bolus injections at the dosage of 90–120 μg/kg every 2–3 hours or starting with a higher dose of 270 μg/kg, according to the previous clinical response of the patient. To date, no routine laboratory assay has proven to be helpful for dose optimization of either aPCC or rFVIIa treatment, hence careful clinical follow-up is mandatory in order to avoid bleeding complications.

Conclusions

Radioactive synoviorthesis offers the possibility of delaying the evolution of synovitis into chronic arthropathy in haemophilic patients. Neither open surgery nor large amounts of concentrate are necessary. Hence, radioisotopic synoviorthesis should be preferred, especially in inhibitor patients. It allows to obtain complete synovial fibrosis, usually in one session, without the need for repeated injections. Thus, RS reduces the risk of bleeding complications and concentrate consumption. For this reason, nuclear medicine national programmes (18) should be implemented and supported, particularly in developing countries. Nevertheless, surgical synovectomy is indicated when three consecutive synoviortheses (repeated every 3 months) fail to halt synovitis.

Conflict of interest

All authors declare that there is no conflict of interest.

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