Chapter 9

Feasibility of double blind intra-articular fluid administration in the temporomandibular joint: a case report

Submitted

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Abstract

Objective The aim of this case study was to investigate the feasibility of a standardized, double blind technique for intra-articular administration of highly viscous sodium hyaluronate or placebo using a mechanical syringe pump to eliminate perceptive information bias.

Methods A 41-year-old woman with a history of TMJ pain, which persisted for more than two years despite of several treatments, participated in this study. Intra-articular administration of hyaluronate and placebo fluid was performed using a mechanical pump in order to achieve standardized application. The treatment consisted of five intra-articular injections with a weekly interval. Out of the five injections, four injections consisted of sodium hyaluronate and one of isotonic saline. The patient and the treating clinician were blinded for the content of the injection. After each session, the patient and the treating clinician were asked whether they thought sodium hyaluronate or isotonic saline had been administered. A diary was kept to register discomfort induced by the treatment. Prior to the treatment and three months post treatment TMJ pain was scored using a visual analogue scale, maximum mouth opening was measured, and functional impairment was scored using the Mandibular Function Impairment Questionnaire.

Results For three of the five times a sufficient flow could be established. Neither the treating clinician nor the patient could determine afterwards during which session placebo was applied. Reported discomfort consisted of transient stiffness and mild swelling, and temporary pain increase. Three months post treatment the pain score was reduced from 80 to 22. Maximum mouth opening remained about the same (63 to 65), and mandibular function improved considerably (84 to 34).

Conclusions It seems feasible to use a mechanical syringe pump to administer highly viscous hyaluronan into the TMJ cavity in a double blind placebo controlled study design.
Introduction

Intra-articular administration of fluid into the temporomandibular joint (TMJ) is an important topic in contemporary research of treatment modalities for TMJ pathology, especially in cases where conservative therapy has been insufficient. Several substances can be applied to the joint in order to re-establish rheology, increase joint mobility, reduce pain and inflammation or provide for improvement of the distribution of nutritional factors. One of the substances of current interest is hyaluronic acid. In large synovial joints, such as the knee but also the ankle, application of this substance has shown to be superior in the treatment of osteoarthritis with regard to pain relief and function improvement. However, with regard to minimally invasive treatment of the TMJ there is a paucity of high-level evidence. In order to determine the effectiveness of intra-articularly applied substances in the TMJ, a double blind, placebo controlled randomized trial of sufficient power is preferred. But, due to differences in viscosity between hyaluronic acid and placebo (otherwise the placebo fluid may have a therapeutic effect itself), blinding of especially the clinician, who receives perceptive information during injection, is difficult to establish. Bertolami et al. reported a randomized, double blind, placebo controlled trial on this topic, but how blinding of the patients and the clinician was obtained was not mentioned. Guarda-Nardini et al. performed a pilot study to the efficacy of arthrocentesis combined with viscosupplementation. However, this study lacked a (placebo) control group, and neither the patients nor the treating clinicians were blinded. Nevertheless, the results were promising. Therefore, it seems worthwhile to develop an application technique that enables researchers to investigate the effectiveness of hyaluronic acid application in the TMJ in a double blind, placebo controlled study design. However, to be able to do so, it is necessary to administer a highly viscous fluid or less viscous placebo in a double blind manner. Administration using a syringe and hand force provides perceptive information. Therefore, differences in viscosity between highly viscous hyaluronate and a less viscous placebo fluid can easily be detected. However, trying to solve this problem by using a placebo fluid of similar viscosity may result in a therapeutic effect of the placebo fluid itself. Therefore, the aim of this case study was to investigate the feasibility of standardized, double blind intra-articular administration of sodium hyaluronate or placebo using a mechanical syringe pump to eliminate perceptive information bias.

Materials and methods

Case description

In March 2009, a 41-year-old woman was referred to the department of oral and maxillofacial surgery of the University Medical Center Groningen (UMCG), the Netherlands, with increasing pain and clicking sounds in her right TMJ after physical violence. After diagnostic local anaesthesia of the TMJ (Ultracain forte, Aventis Pharma, Hoevelaken, The Netherlands), the pain had completely disappeared, indicating that the pain was primary arthrogenic. Initially the patient was treated conventionally. First the patient was instructed to use a soft diet. Thereafter splint therapy was applied and in November 2009
the patient received arthrocentesis. However, the applied therapies did not reduce the pain sufficiently (according to the patient’s perception approximately 25% pain reduction). Because the pain did not cease over time, in February 2011, the patient returned to the department and was then asked to participate in the present study. Approval of the ethical committee of the UMCG was obtained prior to patient recruitment (METc 2009.181), and the patient signed a written informed consent.

**Treatment procedure**
The treatment consisted of five intra-articular injections with a weekly interval, based on the successful protocol for the treatment of osteoarthritis in the knee joint. Prior to each injection, analgesia of the TMJ was achieved by local anaesthesia (Ultracein forte, Aventis Pharma, Hoevelaken, The Netherlands). Thereafter, an 18 gauche needle was inserted into the upper joint compartment. A syringe with isotonic saline was connected, and a pumping motion was used to confirm the position of the needle. After correct placement, the needle was kept in place by the treating clinician, and a syringe that contained sodium hyaluronate or placebo replaced the syringe with isotonic saline. Four of the five injections consisted of sodium hyaluronate (1%) and one of isotonic saline (placebo). All five times, the content of the syringe was administered to the joint cavity using a mechanical syringe pump (Omnifuse syringe pump, Smith Medical MD Inc, St Paul, U.S.A.), which was preset at administrating 0.7 ml fluid at 3.0 ml/h. The patient and the treating clinician were ignorant of the content of the syringe. After each session, the patient and the treating clinician were asked whether they thought sodium hyaluronate or isotonic saline had been administered. During the treatment period of five weeks, the patient was asked to keep a diary and write down how she had experienced the treatment in terms of pain and discomfort. Prior to the treatment and at the follow-up assessment three months post treatment, the patient was clinically scored for pain intensity in the TMJ using a visual analogue scale (VAS, 0-100mm), and maximum mouth opening (MMO, inter incisor distance in mm). Furthermore, functional impairment was scored using the Mandibular Function Impairment Questionnaire (MFIQ, score 17-85). Also X-rays were recorded in order to detect any bony changes.

**Outcomes**
Primary outcome was the feasibility of viscosupplementation administered by a mechanical pump. Besides the technical feasibility, the subjective impact of the treatment was registered using a diary.

Secondary outcome measurements were pain in the TMJ (VAS, 0-100mm), Maximal mouth opening (MMO, inter incisor distance in mm) and functional impairment (MFIQ).

**Results**

Three of the five times (session 1, 2 and 4) a sufficient flow could be established to administer the pre-set 0.7 ml. During the other two sessions the accumulated resistance
of the high-pressure line and the intra-articular pressure exceeded the pre-set safety limit of the pump, and therefore the 0.7 ml was not administered completely. During one of the five times placebo was applied. Neither the treating clinician nor the patient could determine afterwards during which session placebo was applied. After the first session the patient reported stiffness, no pain reduction and minor swelling of the TMJ. After the second session the pain had disappeared and no stiffness or swelling were reported. However, after the third session the pain had returned. Following the fourth session the patient reported again transient swelling, but less pain compared to the previous session. After the final session the patient did not report any discomfort.

At the follow-up, three months post treatment, there was a pain reduction from VAS 80 to 22, MMO remained about the same (63 to 65), and function impairment improved considerably (MFIQ score 84 to 34).

Discussion

The results of this study suggest that it may be technically possible to use a mechanical pump to administer sodium hyaluronate or isotonic saline in a double blind manner. Furthermore, patient discomfort induced by this treatment procedure seems comparable to other minimally invasive techniques such as arthrocentesis. Although only one patient was treated, in this relatively severe case, viscosupplementation seems to have been effective in reducing pain and mandibular function impairment.

During two of the five sessions the pre-set volume of 0.7 ml was not completely applied because of insufficient flow. Hereby, the resistance of the high-pressure line plus the intra-articular pressure exceeded the pre-set safety limit of the pump. The syringe pump used in this study was not originally designed for intra-articular administration. However, results from fresh frozen human cadaver experiments prior to this case study suggested that the safety limit was accurate. Probably the resistance of the high-pressure line has a major contribution to the pressure accumulation. This type of line was preferred because of its inextensibility and its small lumen, which allowed precise bolus administration. Shortening this line may induce a sufficient decrease of the required administration pressure. Furthermore, the needle was kept in place by the treating clinician, which may have allowed the needle to displace unperceived from the joint cavity. Additionally, an optimal volume of the bolus has not yet been determined. Therefore, these two injections may have been sufficient depending on the optimal bolus.

The history of this case indicated a long period of TMJ pain (more than two years), and several unsuccessful non-invasive and minimally invasive therapies. By definition this is a case of chronic TMJ pain. Chronic pain involves neurologic adjustments and behaviour modification, as well as changes in pain perception. Therefore, a considerable pain reduction or improvement of function impairment was not likely to occur. However, in this case these improvements did occur. Possibly these results may be mainly the result of four time hyaluronan application. However, this case study was not designed to investigate the effectiveness of viscosupplementation. Therefore variables like local anaesthetics and
the position check of the administration needle with isotonic saline may have contributed to the clinical outcomes as well.

The aim of this case study was to investigate the feasibility of standardized, double blind intra-articular administration of sodium hyaluronate or placebo using a mechanical syringe pump to eliminate the perceptive information bias. Although this technique was used in the treatment of only one patient, the results seem promising. In this study intra-articular administration was performed five times. However, further research is needed to determine the optimal bolus volume of repetitions with regard to treatment effect and patient discomfort. Furthermore, the use of a mechanical syringe pump allows double blind testing of a variety of substances to be administrated intra-articularly. This may be very useful in future studies investigating the effectiveness of intra-articular therapeutic substances.

Conclusions

Based on the results of this case study, it seems feasible to use a mechanical syringe pump to administer highly viscous hyaluronate into the TMJ cavity. Hereby, perceptive information about the viscosity of the applied fluid is eliminated. Therefore, this administration technique may be useful in future research with a double blind placebo controlled design, investigating the efficacy of intra-articularly applied substances.
References


