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Effectiveness of Dexamethasone Iontophoresis for Temporomandibular Joint Involvement in Juvenile Idiopathic Arthritis

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Abstract

Objective—Temporomandibular joint (TMJ) involvement is common in Juvenile Idiopathic Arthritis (JIA). Dexamethasone iontophoresis (DIP) uses low-grade electric currents for transdermal dexamethasone delivery into deeper anatomic structures. The purpose of this study was to assess the safety and effectiveness of DIP for the treatment of TMJ involvement in JIA, and to delineate variables that are associated with improvement after DIP.

Methods—Medical records of all JIA patients who underwent DIP for TMJ involvement at a larger tertiary pediatric rheumatology center from 1997 to 2011 were reviewed. DIP was performed using a standard protocol. The effectiveness of DIP was assessed by comparing the maximal inter-incisor opening (MIO_{TMJ}) and the maximal lateral excursion (MLE_{TMJ}) before and after treatment.

Results—Twenty-eight patients (ages 2– 21 years) who received an average of eight DIP treatment sessions per involved TMJ were included in the analysis. Statistically significant improvement in the median MIO_{TMJ} ($p< 0.0001$) was observed in 68%. The median MLE_{TMJ} ($p= 0.03$) improved in 69%, and resolution of TMJ pain occurred in 73% of the patients who had TMJ pain at baseline. Side effects of DIP were transient site erythema (86%), skin blister (4%), and metallic taste (4%). Improvement in TMJ range of motion from DIP is associated with lower MIO_{TMJ}, lower MLE_{TMJ}, and absence of TMJ crepitus at baseline.

Conclusion—In this pilot study DIP appeared to be an effective and safe initial treatment of TMJ involvement in JIA, especially among patients with decreased TMJ measurements. Prospective controlled studies are needed.

Key Terms

JIA; TMJ; iontophoresis

INTRODUCTION

In about 30–80% of children and adolescents with Juvenile Idiopathic Arthritis (JIA) the temporomandibular joint (TMJ) is affected[1–3]. Besides pain, swelling, and limitation in the range of motion, TMJ arthritis can present with headaches, neck pain, and pain with mastication. If untreated and persistent, TMJ arthritis can result in micro-retrognathia, facial asymmetry and, therefore, decreased quality of life[2,3].

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Despite the effectiveness of currently available treatments for JIA in general, the best and safest treatment for a child with TMJ arthritis in isolation or when present with peripheral arthritis has not been well studied[4–8]. Intra-articular steroid injections for TMJ arthritis in JIA have been shown to improve TMJ range of motion and improvement of TMJ inflammation on magnetic resonance imaging (MRI)[9–11].

However, intra-articular steroid injections to the TMJ are not without drawbacks. Generally, procedural sedation is required, possibly lipoatrophy at the injection site can occur, and TMJ avascular necrosis has been reported[3,9,11–13]. Likewise, intra-articular steroid injection to the TMJ is usually performed by interventional radiologists as only a few pediatric rheumatologists have acquired the procedural expertise of intra-articular steroid injection to the TMJ as part of their training.

Conversely, dexamethasone iontophoresis (DIP) is a non-invasive physiotherapy modality which allows for transdermal delivery of dexamethasone[14]. Low-grade electric currents lead to the dissociation of hydrophilic medications into ions which move to penetrate deeper anatomic structures[15]. DIP therapy has been utilized for more than 30 years to treat various musculoskeletal conditions including tendinitis, epicondylitis, enthesitis, and inflammatory peripheral arthritis[16–19]. Given the relatively superficial position of the TMJ, we hypothesized that DIP is beneficial for the treatment of the TMJ of children with JIA.

This pilot study aimed (1) to assess the effectiveness and safety of DIP when used for the treatment of TMJ involvement in JIA, and (2) to delineate variables that are associated with improvement after DIP.

MATERIALS AND METHODS

Demographics and Clinical Data

With approval of the institutional review board, patients with TMJ involvement and JIA who underwent the procedure 'dexamethasone iontophoresis' from 1997 to 2011 were identified from the electronic medical record (EMR) and billing databases of the Division of Occupational and Physical Therapy at Cincinnati Children's Hospital Medical Center (CCHMC). Data extraction was performed by RM, PM and SP.

For each patient the EMR was reviewed for gender, JIA subtype, activity of JIA as measured by the number of joints with active arthritis, medication prescribed for the treatment of JIA, duration of JIA, and markers of systemic inflammation [erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)]. We also recorded the patient's age at the time of DIP, duration of TMJ involvement prior to DIP, and DIP treatment period (i.e. number of days from start to final treatment sessions), and the number of DIP sessions. Adherence to the prescribed DIP treatment schedule was also noted.

Assessment of TMJ involvement—Two anatomical measurements were obtained routinely by the physical or occupational therapist. These were: (1) the maximum inter-incisal opening (MIO_{TMJ}), defined as the distance (in mm) between the upper incisor and the lower incisor on full mouth opening with neutral head position, and (2) the maximum lateral excursion (MLE_{TMJ}), defined as the maximum horizontal distance (in mm) that is measured between the upper and lower central incisors (or between the lip frena) with excursion of the mandible to the left or the right side, respectively. The MIO_{TMJ} and MLE_{TMJ} measurements were performed using the *TheraBite range of motion scale* (Atos Medical, Milwaukee, WI).

About 60% of the measurements were done by a one physical therapist (PM). Based on previous studies, the MIO_{TMJ} and MLE_{TMJ} have excellent inter-rater and intra-rater reliability. The intraclass correlation coefficient $(ICC)_{inter\text{-}rater}$ for MIO_{TMJ} and MLE_{TMJ} are 0.9 and 0.77, respectively, while the $ICC_{intra\text{-}rater}$ are 0.87 and 0.85, respectively[20,21]. Earlier research suggested that decreased TMJ range of motion is a good surrogate measure (sign) of TMJ arthritis in JIA[22,23].

We recorded whether TMJ findings were unilateral or bilateral. We also documented the presence (versus absence) of symptoms and signs associated with TMJ involvement. They are TMJ pain when chewing, TMJ pain at rest, clicking and crepitus on TMJ examination. The results of MRI and x-ray studies of the TMJ done within three months of the initial and final DIP sessions were also reviewed.

Procedure - Dexamethasone Iontophoresis

DIP was administered by a trained physical or occupational therapist. The standard protocol consisted of eight to 10 DIP sessions. Time intervals between DIP sessions were one to three days for the initial four to six sessions; thereafter, the frequency of DIP was decreased to once weekly. Fewer sessions were done if the treatment goal of inducing maximal improvement of the TMJ range of motion (MIO_{TMJ} and MLE_{TMJ}), and/or resolution of TMJ symptoms and signs was met.

The iontophoresis equipment (Dupel, Empi, St Paul, MN) that was used for DIP featured bipolar electrodes (*see* Figure 1), the drug delivery and the dispersive electrode (IOGEL®, IOMED Inc; Salt Lake, UT). The delivery electrode was prepared by adding 1.5 mL of dexamethasone sodium phosphate (total dose 6 mg of dexamethasone per TMJ per session). The skin over the TMJ was cleaned with alcohol prior to the placement of the delivery electrode which was connected to the negative pole of a direct current (DC) generator. The dispersive electrode was placed over the trapezius or biceps muscle on the same side of the body as where the delivery electrode was positioned, and connected to the generator's positive pole. Typically, the electrical current was initiated at 0.5 milliamperes (mA) for the initial 30 seconds of treatment session. After a slow increase as per patient's tolerance, the electric current was maintained at the highest tolerable level for patient comfort, usually at 4 mA. Settings of the iontophoresis equipment ensured that the current flow continued for a total constant current dose of 40 mA · min which allowed for the entire dexamethasone dose to be administered. Drug delivery was typically achieved over 15 to 30 minutes. After the procedure the electrodes were removed and the skin inspected for signs of irritation.

Statistical Analysis

Descriptive statistics was done using medians and inter-quartile ranges (IQR) for numeric variables, and frequencies (percentages) for categorical data. The *primary outcome variable* to assess the effectiveness of DIP was the change (in mm) of the MIO_{TMJ}, and the other primary outcome variable was the change in MLE_{TMJ}. For the purpose of the analysis we averaged the measurement of the MLE_{TMJ} for the left and right excursion when bilateral involvement was present. The absolute MIO_{TMJ} and MLE_{TMJ} measurements at baseline were compared to the corresponding final MIO_{TMJ} and MLE_{TMJ} measurements after the last DIP session using Wilcoxon signed-rank test. Resolution of TMJ chewing or resting pain was also evaluated.

Furthermore, the *response to DIP therapy* (yes/no) was defined as achievement of a normal age-adjusted MIO_{TMJ} or MLE_{TMJ}[24,25] upon completion of the DIP treatment course. Exploratory analyses focused on the presence versus absence of any *improvement* in the MIO_{TMJ} or MLE_{TMJ} measurements upon completion of the DIP therapy.

To identify variables that are associated with improvement to DIP, spearman correlation was performed using the change in the MIO_{TMJ} or the change in the MLE_{TMJ} as dependent variable. Variables considered univariately were the number of DIP sessions, bilateral TMJ signs/symptoms (yes/no), number of joints with active arthritis, duration of TMJ involved, JIA disease duration, baseline TMJ resting or chewing pain (yes/no), baseline TMJ click (yes/no), baseline TMJ crepitus (yes/no), JIA subtype, patient's age at time of DIP, and presence/absence of concomitant medications. Statistical analysis was done using SAS 9.2 software (Cary, NC) and R software (www.r-project.org). P-values ≤ 0.05 are considered statistically significant.

RESULTS

Patients

Among 32 JIA patients who underwent DIP for TMJ involvement, four patients were excluded from the subsequent analysis because there was only a single MIO_{TMJ} recorded for each of these patients despite multiple DIP therapy sessions. Twenty-eight patients had serial MIO_{TMJ} measurements, and for 16 of the 28 patients MLE_{TMJ} measurements were available. Details on the patient population are provided in Table 1. All subtypes of JIA except for the undifferentiated subtype were represented. Five patients tested positive for antinuclear antibody, and two patients had abnormal ESR and CRP at baseline. Medication regimens remain stable during the DIP treatment period. None of the patients had undergone TMJ intra-articular steroid injections prior to receiving DIP. No other therapeutic modality for the TMJ was prescribed to the patients during the treatment period.

TMJ Involvement—The most common indications for DIP included decreased TMJ range of motion and TMJ pain. At baseline, ten patients (10/28=36%) and nine patients (9/16=56%) had normal age-adjusted MIO_{TMJ} and MLE_{TMJ}, respectively. Among the 28 patients, DIP was performed bilaterally in 54% and unilaterally in the others. The median number of DIP sessions was 8 ± 1 (range: 2–14) and the median treatment period was 33 ± 17.5 days (range: 7–74 days).

Adherence to the DIP therapy was seen in 27 (96%). One patient received only two DIP sessions and discontinued the treatment for unknown reasons.

MRI and X-ray Imaging—For seven patients a contrast MRI study of the TMJ was done prior to DIP therapy. Findings included condylar flattening (n=5), condylar erosions (n=3), synovial effusion (n=3), synovial hypertrophy (n=4), and synovial enhancement (n=6). Only one patient had a panoramic x-ray done prior to receiving DIP therapy, which showed condylar flattening.

Response to DIP therapy

Upon completion of DIP therapy, the median increase in the MIO_{TMJ} and in the MLE_{TMJ} was 4.5 mm (p-value<0.0001) and 2.25 mm (p-value=0.01), respectively (*see* Table 2).

Nineteen of 28 patients (68%) experienced some increase in their MIO_{TMJ}. There was a median increase of 5 mm with DIP in the MIO_{TMJ} of 18 patients with abnormal MLE_{TMJ} at baseline (p-value<0.0001), while the median increase in the MIO_{TMJ} was only 0.5 mm in the ten patients who had MIO_{TMJ} that was within the age-adjusted range of normal at baseline (*see* Table 3).

In 11 of 16 patients (69%) the MLE_{TMJ} improved with DIP. Also in Table 3, there was a median increase of 3 mm with DIP in the MLE_{TMJ} of seven patients with abnormal

MLE_{TMJ} at baseline (p-value= 0.03), and a small gain in the MLE_{TMJ} by 1 mm in the nine patients who had a MLE_{TMJ} that was within the age–adjusted range of normal at baseline.

Fifteen children included in the study reported pain of the TMJ with chewing and/or at rest, which resolved in 11 of them (73%) with DIP therapy. In addition, pre-treatment TMJ click was reported in seven but resolved in only one patient (14%). Similarly, TMJ crepitus resolved in one of five patients (20%).

Non-Responders of DIP Therapy

About a third of the patients did not experience an improvement in their MIO_{TMJ} and MLE_{TMJ} with DIP. For three patients the post-treatment MIO_{TMJ} or MLE_{TMJ} were smaller than the respective measurements at baseline. A decrease of the MIO_{TMJ} by 1 mm was observed in a 12-year old girl with recently diagnosed very active enthesitis-related JIA but without systemic therapy at the time of DIP. Likewise, despite the resolution of a TMJ click or crepitus, two patients with long-standing oligoarticular JIA who were treated with NSAIDs had a decrease in the MIO_{TMJ} or MLE_{TMJ} from baseline; there was a decrease in the final MIO_{TMJ} in one (i.e. from 50 mm to 46 mm) and in the final MLE_{TMJ} in the other (i.e. from 13.5 mm to 10 mm). Of note, the post-treatment TMJ range of motion measurements remained within the normal range in the latter two patients.

Side Effects of DIP Therapy

Transient non-painful site erythema which lasted for 15 minutes was observed in 24 children (24/28=86%) after DIP sessions. One child (1/28=4%) reported a metallic taste during DIP, and another patient experienced a small skin blister (1/28=4%). The latter occurred in an 18 year old patient after a rapid increase in the intensity of the current flow during her final treatment session (8^{th} session).

Variables associated with improvement after DIP Therapy

Improvement in the MIO_{TMJ} after DIP therapy was associated with lower MIO_{TMJ} ($p<0.0001$), absence of TMJ crepitus (p=0.003) and absence of TMJ click (p=0.02) at baseline. Compared to non-responders, patients who achieved a MIO_{TMJ} within the age-adjusted range of normal were younger [median ± IQR (range): 8 ± 3 years (4–15) *vs.* 15 ± 5 years (8–21), p-value=0.01], and fewer had baseline TMJ pain (38% *vs.* 89%, p-value=0.05). Similarly, lower MLE_{TMJ} (p=0.02) and absence of TMJ crepitus at baseline (p=0.05) were associated with improvement of the MLE_{TMJ} after DIP.

DISCUSSION

To the best of our knowledge this study is the first to evaluate the use of DIP for the treatment of TMJ involvement with JIA. About two-thirds of the patients experienced an improvement or normalization of the TMJ range of motion which was generally accompanied by resolution of TMJ pain.

Despite the lack of its use for JIA-associated TMJ involvement, DIP has been employed for the treatment of arthritis in the past. An earlier pilot study, adult patients with rheumatoid arthritis experienced a reduction in knee pain with DIP to the knee joints[16]. Likewise, Ozgocmen *et al* showed that triamcinolone iontophoresis resulted in a reduction in synovial tissue vascularity on power Doppler sonography, a surrogate for reduced inflammation[18].

The biologic rationale for this modality is based on the principle that like charges repel. In this case, dexamethasone sodium phosphate is a negatively charged ion and is applied to the negative pole (anode) of the bipolar iontophoresis set-up; electrical charge applied to the

anode forces the drug ions to be pushed through the skin into the deeper tissues. In a study evaluating tissue penetration of iontophoretically administered dexamethasone in rhesus monkeys, dexamethasone was demonstrated in all tissues underlying the electrode down to, and including, tendinous structures and cartilaginous tissues[26].

DIP is associated with a tingling sensation which intensifies with higher electric current flow. The use of a lower current flow to achieve the total constant current dose lengthens the treatment time but minimizes this tingling sensation. DIP is appealing for use in JIA since it is painless, non-invasive, and can be performed without sedation. None of the patients developed skin or soft tissue atrophy during the follow-up period.

Intra-articular steroid injections are also effective to treat TMJ involvement with JIA. Previous studies that evaluated intra-articular steroid injection of the TMJ in JIA patients reported increase in the MIO_{TMJ} that ranged between 1.8 mm and 6.9 mm[9–11,27], measurements comparable to the overall median increase in the MIO_{TMJ} of 4.5 mm observed in our study.

Intra-articular steroid injections, however, carry the risk of avascular necrosis, soft tissue atrophy, and infections[2,9,11–13]. Conversely, iatrogenic infections are virtually impossible with DIP, given its non-invasive nature.

Another advantage of DIP over CT-guided intra-articular steroid injection of the TMJ is that the total direct cost of DIP is likely lower. Based on the review of local billing databases the cost of DIP are about 40% of that of CT-guided intra-articular steroid injection of the TMJ. It remains to be determined how the overall costs, direct and indirect, differ between the two treatment modalities.

Although DIP resulted in statistically significant improvement of the MIO_{TMJ} and MLE_{TMJ}, the clinical relevance of such quite small absolute gains in range of motions in children remains to be determined. Because the minimal clinically significant change in TMJ measurements in JIA patients is unknown, we used age-adjusted normal ranges[24,25] in our secondary analysis to help with the interpretation of the response to DIP therapy.

Not all patients who underwent DIP experienced a therapeutic effect. We hypothesize that non-responders to DIP already had experienced significant TMJ internal derangement or damage which would not be expected to improve in response to non-surgical interventions. This notion is supported by two randomized controlled trials[28,29] of DIP therapy for TMJ internal derangement, capsulitis, and osteoarthritis; one reported an increase in TMJ range-of motion but no difference in pain while the other study suggested stable TMJ range-of motion and improved pain.

Our pilot study has several limitations, including the retrospective nature of the study and the lack of controls. However, data were prospectively recorded using either standardized clinic forms or the EMR, resulting in few missing data for the primary outcome variables of this study. Furthermore, to enhance the quality of data collection[30], there were three abstractors who were all health providers familiar with the measures used in the study.

The selection of patients who underwent the DIP over other treatment modalities may have introduced some bias as well. DIP for TMJ involvement in our institution is usually done based on patient/parental preference. It is also conceivable that the improvement we observed in the patients was partly because of the patients' concomitant systemic medications, which were not controlled in this study. Nevertheless, almost all patients were on stable doses of medications for at least six months before the treatment period, and were actually diagnosed to have TMJ involvement *while* on systemic medications. Persistent TMJ

arthritis despite adequate control of peripheral arthritis has been reported in the past[11]. In our study patients, the presence of concomitant methotrexate or biologic therapy was also not significantly associated with improvement in our correlation analysis.

Ideally, baseline MRI should be done to help assess the degree of inflammation and damage prior to the initiation of DIP therapy, and additional imaging would be desirable to confirm the resolution of inflammation after completion of DIP. Routine serial MRI was not performed in our clinical setting due the need for sedation in the young patients and the substantial cost of MRI. In this study, we considered the increase of TMJ range of motion (MIO_{TMJ} and MLE_{TMJ}) as surrogate of TMJ inflammatory changes in JIA[22,23].

In conclusion, we found DIP to be an effective and safe treatment modality for JIA patients who have TMJ involvement, especially among those with abnormally low TMJ range of motion measurements and without TMJ crepitus at baseline. Further research is required to determine the optimal number of DIP sessions based on sensitive imaging approaches, durability of treatment response, and performance of DIP in direct comparison to intra-articular steroid injection for the TMJ.

SIGNIFICANCE AND INNOVATION

1. Dexamethasone iontophoresis (DIP) is a novel treatment modality for temporomandibular joint (TMJ) involvement in Juvenile Idiopathic Arthritis (JIA).
2. Based on historic information, the effectiveness of DIP is comparable to intra-articular steroid injection of the TMJ.

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Figure 1. Dexamethasone iontophoresis of the temporomandibular joint

Panel 1a depicts the iontophoresis equipment with its two bipolar electrodes. On the top is the oval delivery electrode which has the dexamethasone reservoir directly below the clamp. On the bottom is the square dispersive electrode. The iontophoresis device shows the total current dose to be administered. The dials on top of the iontophoresis device are used to adjust the level of current flow intensity.

Panel 1b shows the placement of the two electrodes during DIP sessions. The delivery electrode is placed on the involved TMJ and the dispersive electrode on the upper arm at the same side of the treated TMJ.

Table 1

Demographics and Clinical Data (n=28)

	Number (% of Total)	Median ± IQR (range)
Age (years)		13 ± 8.5 (2–21)
Female/Male	23 (82%)/5 (18%)	
Race: Caucasian/African-American/Asian	26 (93%)/1 (4%)/1 (4%)	
JIA subtype		
Enthesitis-related	2 (7%)	
Oligoarthritis extended	1 (4%)	
Oligoarthritis persistent	8 (29%)	
Polyarthritis RF negative*	11 (39%)	
Polyarthritis RF positive	2 (7%)	
Psoriatic	2 (7%)	
Presence of uveitis	5 (18%)	
Medications		
NSAIDs∫	22 (79%)	
Methotrexate	10 (36%)	
Any biologic	8 (29%)	
Prednisone	1 (4%)	
Number of active joints		6 ± 8 (1–16)
Duration JIA (months)		24 ± 41 (4–84)
Duration of TMJ disease (months)		3 ± 12.5 (1–24)

* RF: Rheumatoid factor,

∫ NSAID: Non-steroidal anti-inflammatory drugs

Table 2

Improvement of the range of motion of the temporomandibular joint with dexamethasone iontophoresis[†]

Measurements	Number of Subjects	Pre-therapy	Post-therapy	P-value[¶]
Maximal inter-incisor opening (MIO_{TMJ})	28	35 ± 14 (20–55)	39.5 ± 10.5 (26–55)	<0.0001
Maximal lateral excursion (MLE_{TMJ})	16	7.75 ± 3.25 (2–20)	10 ± 2 (6–20)	0.01

[†]Values are median ± IQR (range) in mm

[¶]P-value for the association of MIO and MLE pre and post-therapy

Table 3

Improvement of the range of motion of the temporomandibular joint (TMJ) with dexamethasone iontophoresis under consideration of age-adjusted norms[†]

Measurements	Number of Subjects	Pre-therapy	Post-therapy	P-value[¶]
Patients with baseline TMJ measurements below age-adjusted norms				
Maximal inter-incisor opening (MIO_{TMJ})	18	32 ± 10 (20–38)	37 ± 5 (26–46)	<0.0001
Maximal lateral excursion (MLE_{TMJ})	7	5.5 ± 3 (2–7.5)	8.5 ± 3 (6–10.5)	0.03
Patients with baseline TMJ measurements within age-adjusted norms				
Maximal inter-incisor opening (MIO_{TMJ})	10	45.5 ± 10 (30–55)	46 ± 10 (38–55)	NS[∫]
Maximal lateral excursion (MLE_{TMJ})	9	9 ± 5 (7.5–20)	10 ± 2.5 (7.5–20)	NS

[†] Values are median ± IQR (range) in mm

[∫] NS: not significant

[¶] P-value for the association of MIO and MLE pre and post-therapy