CLINICAL, LABORATORY AND COLOR Doppler ultrasonography study of synovitis in rheumatoid arthritis

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KEY WORDS: COLOR DOPPLER ULTRASONOGRAPHY, SYNOVITIS, RHEUMATOID ARTHRITIS.

ABSTRACT

Objective: To evaluate the use of color Doppler ultrasonography (US) analysis of the synovial membrane vascularisation and its relation to clinical and laboratory manifestations of rheumatoid arthritis patients before and after intra-articular treatment with glucocorticoids in target joints.

Methodology: This study was carried on 30 RA patients who were suffering from one or two joints flare up, thus intra-articular glucocorticoids injection may help to control their condition. The included joints were 18 wrists and 12 knee joints. Clinically, the patients were assessment by calculating the mean of the articular index score for the patients, by measurement the mean of morning stiffness for them, then disease activity in target joint was estimated clinically by target joint pain on 100mm visual analogue scale (VAS), swelling and tenderness in target joint (which were scored 0-3). Laboratory investigations especially erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) which were performed for all patients.

Ultrasonographic examination: the target joint was scanned by grey mode US and synovial thickness was graded (from 0 to 3), and it was scanned by color Doppler US and resistive index (RI) was calculated as (peak systolic flow - end diastolic flow) / peak systolic flow, thus sonographic guided intra-articular injection of methylprednisolone was done.
Clinical, laboratory and sonographic examinations were carried out before and also 4 weeks after injection.

**Results:** There were highly significant difference in morning stiffness (MS), VAS, swelling tenderness, synovial thickness and RI before and 4 weeks after injection ($p<0.001$). As regards to activity in target joint, there was a significant negative correlation between RI and swelling & tenderness ($p<0.05$), and a highly significant negative correlation between it and VAS ($p<0.001$) before and after injection. But synovial thickness showed only a significant correlation between it and swelling & ESR 4 weeks after injection ($p<0.05$). Other clinical, laboratory and activity parameters in target joint showed non significant correlation between them and RI or synovial thickness.

**Conclusion:** Color Doppler US were found to be helpful in detection of response to local treatment with intra-articular corticosteroids and aid in making therapeutic decision. Also, the RI and synovial thickness are able to detect a treatment with corticosteroids; changes in RI are parallel to changes in clinical evaluation of RA disease. Thus, imaging assessment may be necessary for the accurate evaluation of disease status and in particular, for the definition of true remission.

**INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the development of synovitis, which damages cartilage, bone, ligaments, and tendons (Naredo et al., 2005).

The primary site of pathology in RA is the synovium of joints, the synovial tissues become inflamed and proliferated, forming pannus that invades bone, cartilage and ligament and leads to damage and deformities (Hitchon & El-Gabalawy 2003).

Vascularisation of the synovial pannus appears to be crucial to its invasive and destructive behavior and correlates with disease activity (Carotti et al., 2002).

Ultrasonography (US) offers a non-invasive, reproducible, non-radiating and relatively inexpensive method to detect joint effusion and
bursal fluid collection and may detect hyperplastic synovium and underlying erosive disease (Grassi, et al., 2001).

Conventional US, however, do not provide color maps of tissue or direct information about hemodynamics alternations, which may occur in soft tissue inflammation. With modern high quality sonographic equipment, color / power Doppler can be used to determine the flow even in small blood vessels. This again, may be helpful in evaluating the inflammatory activity and efficacy of the therapeutic regimens (Schmindt, et al., 2000).

Local therapy, including intra-articular injection of corticosteroid, is indicated when there are joints with persistent disease activity despite adequate systemic control of the disease. During the course of RA, it is frequently found that, although systemic inflammatory disease activity is controlled with the use of DMARDs (disease modifying antirheumatic drugs) and anti-inflammatories (steroidal and non steroidal), some joints still active inflammation. In this situation intra-articular corticosteroids injection is used to relieve synovitis in target joint (Tomas, et al., 2000).

**Aim Of The Work:**

To evaluate the use of color Doppler US analysis of the synovial membrane vascularisation, and its relation to clinical and laboratory manifestations of rheumatoid arthritis patients, before and after treatment with glucocorticoids in target joints (knees& wrists).

**PATIENTS AND METHODS**

This study was carried on 30 RA patients (7 males, 23 females) who were attending the outpatient & inpatient clinic of rheumatology and rehabilitation department, faculty of Medicine, Zagazig University Hospitals. They diagnosed as revised ACR criteria for the classification of RA (Arnett, et al., 1988). Their ages ranged from 21 to 55 with a mean ± SD of 33.8 ± 8.93 years. The disease duration range from 6 months to 12 years with a mean ± SD of 4.37 ± 3.06 years.

All the patients were suffering from one or two joints flare up, thus intra-articular glucocorticoids injection may help to control their condition. The included joints were 18 wrists and 12 knee joints. For at least three months before the study all patients were receiving stable disease modifying antirheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) treatment.

During the observation period of four weeks their drugs were unchanged and no further injections were given. None of the patients
received oral glucocorticoid treatment in doses more than 7.5 mg. Daily. None of the patients received intra-articular glucocorticoid injection in the target joint for at least six months before the study.

**All patients were subjected to the following:**

* Complete history taking (with stress on the duration of morning stiffness in minutes).
* Thorough clinical examination with stress on:
  - Locomotory system examination.
  - Assessment of joint tenderness by the Ritchie articular index score (*Ritchie et al., 1968*).
* Activity in target joint: Disease activity was estimated clinically according to *Terslev et al. (2003)* at base line and 4 weeks after intra-articular injection with methylprednisolone acetate by:
  1. Target joint pain on a 100 mm visual analogue scale.
  2. Swelling in target joint was scored 0-3.
  3. Tenderness in target joint was scored 0-3.
* Laboratory investigations:
  - Routine laboratory tests: ESR (1 st hour), CRP and complete blood picture.
  - Latex agglutination slide test for detection rheumatoid factor.
* **Ultrasonography and color Doppler examinations:**

**Instruments:** The target joint was scanned immediately after the clinical examination by Nemu 20 Toshiba using a linear transducer with a frequency 5-10 MHZ.

**Technique:** The target joint was scanned at predefined transducer positions for that particular joint and the synovial membrane was examined longitudinally and transversally. Blood flow in the synovial membrane was visualized with color Doppler ultrasonography.

Doppler setting was standardized with a color-mode frequency of 5-9 MHZ. Wall filters was set at the lowest value.

Each joint was explored for the highest level of expression of signs of synovitis, using a multiplaner examination according to the standard scanning protocol reported in the guidelines for musculoskeletal sonography (*Backhaus, et al., 2001*).

-Synovial thickness was graded on the same scale used by *Carotti, et al. (2002)*:
* 0: for thickness <2 mm.
* 1: for thickness range from 2 to 5 mm.
* 2: for thickness range from 6 to 8 mm.
* 3: for thickness > 8 mm.

Three random synovial arteries were sampled in this way: The ultrasound unit traced the Doppler spectra electronically and identified the cardiac cycles as well as peak systolic flow and end diastolic flow. The unit then calculated the resistive index (RI) as (peak systolic flow - end diastolic flow) / peak systolic flow.

**Injection:**

All injections were carried out guided by ultrasound. The ultrasound probe was held just outside the injected site but with a clear view of the area of interest. Using non touch technique, the needle was then inserted into the joint cavity visualized on ultrasound to ensure correct placement of the needle.

The injection was done in the knee joint through the lateral retropatellar approach, and the injection in the wrist joint was done through the radial approach (NcRae, 2004).

Clinical and sonographic follow up examinations were carried out 4 weeks after the sonographic guided intra-articular injection with methyprednisolone acetate, with particular attention being paid to reproducing the base line scanning approach.

Data were coded, entered and checked to an SPSS (statistical package for social science) (Nuresis MJ, 1997).

**RESULTS**

Our study was carried on 30 RA patients, 7 males (23.3%) and 23 females (76.7%) with mean age ±SD 33.3 ±8.93 years. They suffered from the disease with the mean duration ± SD of 4.37 ±3.06 years ago.

Our patients were examined before and 4-weeks after intra-articular injection of glucocorticoids, their clinical and laboratory data were shown in table (1):
From this table it was found that there were highly significant difference as regards morning stiffness (MS), VAS, swelling and tenderness before and after 4 weeks of intra-articular injection of glucocorticoids (p<0.001).

Table (2) shows a highly significant difference before and 4 weeks after intra-articular injection of glucocorticoids for both synovial thickness and RI by grey US and color Doppler US (p<0.001).

This table shows a significant negative correlation between RI and both swelling and tenderness (p<0.05), and highly significant negative correlation between it and VAS (p<0.001), but non significant correlation between it and other clinical & laboratory parameters before and after 4 weeks of intra-articular injection (p>0.05).
Table (3): correlation between RI & clinical, laboratory and parameters of activity in target joint before and 4 weeks after intra-articular injection of glucocorticoids.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before injection</th>
<th>4week after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Swelling</td>
<td>0.41</td>
<td>0.02</td>
</tr>
<tr>
<td>Tenderness</td>
<td>-0.44</td>
<td>0.016</td>
</tr>
<tr>
<td>VAS</td>
<td>-0.49</td>
<td>0.006</td>
</tr>
<tr>
<td>AI</td>
<td>0.21</td>
<td>0.262</td>
</tr>
<tr>
<td>M.S</td>
<td>0.24</td>
<td>0.21</td>
</tr>
<tr>
<td>ESR</td>
<td>0.19</td>
<td>0.313</td>
</tr>
<tr>
<td>CRP</td>
<td>0.08</td>
<td>0.084</td>
</tr>
</tbody>
</table>

Table (4) shows insignificant correlation between synovial thickness and tenderness, VAS, clinical and laboratory parameters before and after injection, but there was a significant correlation between it and swelling & ESR 4 weeks after intra-articular injection of glucocorticoids (p<0.05).

Table (4): correlation between synovial thickness and parameters of activity in target joint, clinical and laboratory parameters before and after 4 weeks of intra-articular injection of glucocorticoids.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Synovial thickness after 4 weeks of injection</th>
<th>Synovial thickness before injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Swelling</td>
<td>0.196</td>
<td>0.299</td>
</tr>
<tr>
<td>Tenderness</td>
<td>0.163</td>
<td>0.39</td>
</tr>
<tr>
<td>VAS</td>
<td>0.148</td>
<td>0.436</td>
</tr>
<tr>
<td>AI</td>
<td>0.23</td>
<td>0.21</td>
</tr>
<tr>
<td>M.S</td>
<td>0.23</td>
<td>0.18</td>
</tr>
<tr>
<td>ESR</td>
<td>0.26</td>
<td>0.17</td>
</tr>
<tr>
<td>CRP</td>
<td>0.152</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Fig. (1): Color Duplex US of right knee before intra-articular injection of glucocorticoids: synovial thickness (A) = 7.6 mm & RI= 0.48.
Fig. (2): Color Duplex US of right knee after intra-articular injection of glucocorticoids: synovial thickness (A) = 3.5 mm & RI= 0.81.
Fig. (3): Color Duplex US of left wrist before intra-articular injection of glucocorticoids: synovial thickness (A) = 6.2 mm & RI=0.34.
Fig. (4): Color Duplex US of left wrist after intra-articular injection of glucocorticoids: synovial thickness (A) = 3.2 mm & RI=0.77.
DISCUSSION

Rheumatoid arthritis is a chronic inflammatory disease with prominent manifestation in the synovial joints characterized by synovial inflammation (Terslev, et al. 2004).

Early changes in the synovium are represented by cell infiltration associated by neovascularization, inflammatory cell infiltration, and synovial hyperplasia which produce a pannus of inflammatory vascular tissue (Carotti, et al. 2002).

As the synovial changes precede more substantial joint damage, it is crucial to detect inflammatory changes early to initiate or change treatment and therapy retarding or stopping the cause of the disease and severe joint destruction. The trend towards earlier aggressive therapy in the arthritis requires reliable diagnosis and optimal disease activity assessment (Schmidt, et al. 2000).

Though it is considered the standard reference for detecting and quantifying the destruction of joints processes, conventional radiography can't reliably detect changes in the synovial membrane. Other imaging modalities like magnetic resonance imaging (MRI) and ultrasound (US) allow this detection of inflammatory changes (Backhaus, et al. 1999).

This study was performed to evaluate the use of color Doppler US in analysis of the synovial vascularisation and its relation to clinical and laboratory manifestations in patients with rheumatoid arthritis, before and after intra-articular injection with glucocorticoids in target joints (knee or wrist joints).

In our study, there was a high significant difference in morning stiffness and in clinical parameters of activity in target joints (VAS, swelling and tenderness) before and 4 weeks after intra-articular injection of corticosteroid, this is agreement with the results of the studies of (Terslev, et al., 2003 and Filippacci, et al., 2004) and this indicates the efficacy of intra-articular injection of corticosteroid in controlling disease activity in target joints.

We found also a high significant increase in RI and decrease in the thickness of synovium (p<0.001) 4 weeks after intra-articular injection with corticosteroids. This is in agreement with Filippucci, et al. (2004) which showed a high significant decrease in power Doppler signals PDS score which was a reflection of diminished flow in the synovium, and also with the results of Terslev, et al. (2003) which indicated also a decrease in inflammatory activity.
In contrast with Terslev, et al. (2003) who reported a significant change in CRP while ESR remained stable, we found non significant change in AI, ESR or CRP. This could be explained by the local effect of the intra-articular corticosteroids. In the present study, there was negative correlation between RI and parameters of activity in target joints: swelling, tenderness (p<0.05) and VAS (p<0.001) before and after 4 weeks of intra-articular injection of corticosteroids. This demonstrate that color Doppler US is reliable tool for estimation of the synovial activity measured by the degree of vascularisation and it may be useful in monitoring the synovial inflammation and the response to intra-articular injection of corticosteroids in RA patients. This is consistent with the findings of (Walther, et al., 2002, Weidikamm, et al., 2003, Strunk, et al., 2004 and Fiocco, et al., 2004) and may be considered in agreement with Koski, et al. (2006) who reported that the reduction of power Doppler signals (PDS) appeared to be related to changes induced by intra-articular injection of corticosteroids. But, this isn't in agreement with (Szkudlarek, et al., 2001 & Qvistgaard, et al., 2001 and Shreif, et al., 2003) who reported the absence of correlation between Doppler US and clinical parameters.

As regards to the correlation between RI and clinical parameters (MS& AI) and laboratory parameters (ESR&CRP) it was non significance either before or after intra-articular injection of corticosteroids (p>0.05).

These results are valid with those of Shreif, (2003), but not with Terslev, et al. (2003) who found significant correlation between Doppler US finding and ESR but not with it and CRP, MS or AI. Also, there was non significant correlation between these parameters and synovial thickness in this study, but the correlation is significant with ESR and it only after 4 weeks of the injection (p<0.05). These results are in accordance with those of (Carotti, et al., 2002 and Qvistgaard, et al., 2001). This could be explained by that parameters reflect multiple joints activity rather than target joint activity; also we selected our patients with one or two joints activity that were in need of intra-articular injection.

In this study, there was non significant correlation between synovial thickness and parameters of target joint activity (tenderness & VAS), before and after intra-articular injection, but there was a significant correlation between it and swelling in this joint after injection (p<0.05). This result was in accordance with the result of Brown, et al. (2006). While, Ficco, et al. (2004) reported a significant correlation between synovial thickness and all parameters of joint activity. While Filippucci, et al. (2004) found that grey scale sonography correlate with tenderness but not with VAS.
This could be explained by the difference between active and inactive pannus, the presence of fibrous tissue within the synovium from previous healed attack of synovitis (Carotti, et al., 2002) and also during disease activity, the swelling in the target joint may be referred to effusion rather than synovial thickness while in case of inactivity the swelling results mainly from synovial thickness (Brown, et al., 2006).

Conclusions:

Color Doppler US was found to be helpful in detection of response to local treatment with intra-articular corticosteroids and aid in making therapeutic decision.

Also, the RI and synovial thickness are able to detect a treatment with corticosteroids; changes in RI are parallel to changes in clinical evaluation of RA disease. Thus, imaging assessment may be necessary for the accurate evaluation of disease status and in particular, for the definition of true remission.

REFERENCES


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دراسة إكلينيكية و معالجية و باستخدام الدوبلر الملون لإنهاءات الغشاء السينوفي في مرضى الرئة المنفصلي

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الهدف: فحص الأوعية الدموية بالغياث البوليسيوني بالدوبلر الملون وعلاقته بالظاهر الإكلينيكية. وتحديد الشروط المفضلة في مرضى الرئة المنفصلي قبل وبعد حقن الكورتيزون داخل منصف المستهدف.

طرق البحث: أجري هذا البحث على 30 مريضاً بالرئة المنفصلي النازعين من نشاط الرئة في منصف أو أثبت أن أثبت الذيل، لذلك فصل حقن المنصف المستهدف بالكورتيزون، وتم العمل على 18 منصف رفيع و12 منصف ركيزة. إكلينيكياً: تم تقييم المرضى حسب معدل الدلالة المفصلية و معدل التحسس البصري لهم، وتم تحديد نشاط الرئة في المنصف المستهدف بحساب مقارنة للدوبلر الملون، ثم حقنه بالكورتيزون تحت ملاحظة الموجات الفوق صوتية.

نتائج البحث: تم اكتساب فروقات ذات دلالة إحصائية بما بين قبل الحقن بالكورتيزون و 4 أسابيع بعد ذلك في كل من التحذير الصبياني و مقدار الألم. ودور المنصف لدى التألم و سمنت الغشاء السينوفي باستخدام الموجات فوق صوتية و معالج المقاومة (أ.ر.أ) داخل الأوعية الدموية باستخدام الدوبلر الملون. كما تم اكتساب علل علاقة عكسية ذات دلالة إحصائية بين مقدار المقاومة داخل الأوعية الدموية و مدى نشاط الرئة داخل المنصف المستهدف. بينما تم اكتساب علاقة ذات دلالة إحصائية بين سمنت الغشاء السينوفي باستخدام الموجات فوق صوتية و مدى تصور المنصف المستهدف. و أيضاً سريعة التحسس بعد 4 أسابيع من الحقن بالكورتيزون. كما تم اكتساب عدد فروقات ذات دلالة إحصائية بين الأعراض الإكلينيكية و المعملية الأخرى وبين معدل مقاومة الحالة، و بين معدل مدا بحالة التحذير.

استنتاج: من هذه النتائج تستطيع أن تصل إلى أهمية الدوبلر الملون في قياس مدى نشاط مرض الرئة المنفصلي و متانا تأثير العلاج بالحقن المنفصلي بالكورتيزون عليه. لذلك تقييم مرضي الرئة المنفصلي بالتحذير بالدوبلر مهم في معرفة حالة المرض و بالخلاص تعريض التحسن الحقيقي له.