Influence of Hyaluronic Acid on the Clinical Course of Ankle Sprains

Christian Jakobs¹; Reiner Wirbel¹; Jan Korner²

1 Department of Trauma-, Hand-, and Reconstructive Surgery, Verbundkrankenhaus Bernkastel-Wittlich, Wittlich, Germany
2 Centre of Orthopaedics, Sports Medicine, and Traumatology, Bodenheim, Germany

Abstract


Introduction: The proven positive clinical effects of hyaluronic acid on intra-articular pathologies may lead to the assumption of similar effects on extra-articular soft tissue structures. Hypothesis: Local application of hyaluronic acid has positive effects on the clinical course of ankle sprains.

Method: Study Design: prospective randomized clinical trial. Forty patients with acute primary ankle sprain of clinical grade I and II and sonographically proven isolated ruptures of the anterior talofibular ligament were randomized in two groups, each n = 20. Group I received standard care including brace immobilisation for 6 weeks; group II also received two periarticular injections of hyaluronic acid, which were administered 24 hours after the injury and two days later. Assessments using the visual analogue scale included rest pain, weight bearing, walking pain, subjective patient satisfaction at primary date, on day 3, and weekly up to the fifth week as well as the period to return to work and sporting activities.

Results: 27 men and 13 women (mean age 30.5, range 16-73 years), 29 athletic injuries, 8 domestic accidents and 3 workplace accidents were observed. In group II, a significant faster pain relief and higher patient satisfaction were observed at every evaluation date. The patients in group II could return to work 4 days earlier, on average after 14 days versus 18 days in group I. They also could restart their sporting activities 11 days earlier (23 versus 34 days).

Conclusion: Additional periarticular injection of hyaluronic acid for the treatment of acute ankle sprains leads to a significant faster pain relief, return to work and sporting activities.

Keywords: hyaluronic acid; ankle sprain; efficacy

Introduction:

Ankle sprains are common injuries in both sports and everyday activities. In sporting injuries, the rate of ankle sprains is reported to range from 15 to 20 % [2, 5, 12, 17]. Due to their frequency, ankle sprains have a high economic impact on health care costs. Ankle ligament sprains are usually graded during clinical examination based on the severity of pain, welling, and instability [2]. Grade I is a stretching or partial rupture of the ligaments without severe instability. Grade II represents a partial rupture with moderate pain and swelling. Grade III is a complete rupture with marked pain, haematoma, swelling and impairment of function with instability. When indicated according to the "Ottawa ankle rules", radiographic investigation is required [11]. Besides the clinical test, the talar shift in the sagittal plane and the talar tilt in the coronal plane can also be demonstrated by sonographic investigation [7]. Thus, partial tears such as the rupture of the anterior talofibular ligament can be confirmed with high (>90%) sensitivity. During the last two decades, most studies recommended non-surgical treatment for acute ankle sprains independent upon the severity [3, 4, 12-14]. Surgical treatment is considered to be indicated only in cases of associated lesions such as syndesmosis or cartilage injuries. The choice of surgical repair of ankle ligaments is always based on individual criteria of professional athletes [13]. The conservative treatment usually includes rest, ice, compression, and elevation ("RICE") [3]. Immobilization by use of a cast in cases of grade III injuries and massive swelling, consequent ankle braces up to the sixth week,
and antiphlogistic medication using non-steroidal anti-inflammatory drugs (NSAID’s) or cox-II-inhibitors complete the conservative treatment spectrum [4, 12, 14]. Antiphlogistic medication effectively reduces swelling and pain, however, the clinical course of ankle sprain regarding the return to work or to sports is not influenced. Furthermore, it may contain the risk for adverse events such as gastrointestinal intolerance.

New treatment concepts, such as the application of platelet rich plasma (PRP) or local infiltration with hyaluronic acid, are researched in order to improve conservative treatment [10, 15, 16]. Hyaluronic acid (HA) has proved to have a positive clinical effect on intra-articular pathologies [1, 6]. As HA is considered to modify the rheology of the intra-articular matrix, resulting in positive effects, pain relief and stiffness, possible similar effects on extra-articular soft tissue or ligamentous structures may be assumed.

When looking at the literature, we found only two studies [15, 16], which demonstrated positive effects of local injections of HA on ankle sprains. The short-term results regarding pain relief, swelling and patient’s satisfaction [15] as well as the long-term efficacy regarding the return to sport and re-sprain rate [16] suggest local application of HA. Encouraged by these studies, we wanted to reappraise the effect of HA on acute primary ankle sprains concerning pain relief, return to sport and disability.

Method
The prospective randomized controlled study was arranged between March 2010 and May 2011. The study was approved by the local institutional ethics committee and conducted according to the Declaration of Helsinki Good Clinical Practice guidelines. All patients gave their informed consent prior to participation.

Procedure and study group
Selection criteria
All patients older than 16 years with primary acute (i.e. within 24 hours of administration) ankle sprain of grade I and II were evaluated and clinically examined by the senior consultant (J.K.). Furthermore, the clinical diagnosis was proved by ultrasound using the method described by Ernst et al. [7]. All ultrasonographic examinations were performed by the senior consultant (J.K.). The diagnosis was confirmed by the direct visualization of a haematoma or indirectly by the documentation of the talar shift in the sagittal plane compared with the contralateral side. Only patients with isolated rupture of the anterior talofibular ligament were considered. Radiographic examination was performed according to the “Ottawa ankle rule” [6]. Patients presenting an ankle fracture were excluded.

Treatment Groups
Thus, 40 patients could be enrolled in the study and randomized (1:1) to one of the two treatment groups. The patients of group I received standard care of rest, ice, compression, and elevation (RICE) for two to three days depending upon the swelling and pain relief. Afterwards, external supports were prescribed with an orthosis for 6 weeks to prevent supination. Crutches were used for some days. Weight bearing was allowed depending on the pain. NSAID’s were recommended for analgetic and antiphlogistic medication at patient’s discretion. Physiotherapy was not prescribed.

All patients of group II were additionally treated with local injection of 1.2 ml hyaluronic acid (HA), (SportVis™, recordati Pharmagroup, Ulm, Germany). The technique of the fan-shaped injection around the anterior talofibular ligament was well described by Petrella [15]. All patients of group II received two injections at the first presentation within 24 hours after the injury and two days later. All injections were performed by the senior consultant (J.K.).

Outcome Measures and Follow-Up
The main subject of this research was the decrease in pain using the 10-point visual analogue scale (VAS) [8]. Rest pain, pain on weight bearing and walking as well as general patient satisfaction of the ankle injury were recorded. The VAS was also used to quantify the general satisfaction. VAS score of 0 corresponded to unrestricted daily activities, a score of 10 meant complete immobilization. The periods to return to sports activities and to work were additionally noted. Assessments were done at the primary presentation, on day 3, and weekly up to the fifth week.

Statistical Analysis
We analysed the data using SPSS (version 14.0; SPSS Inc, Chicago, IL, USA) software. Student’s t-test was used to compare the two treatment groups with a 5 % level of significance. A regression co-efficient was ascertained to compare the development of pain relief in the two treatment groups.

Results
There were 27 men and 13 women with an equal male:female representation between the two treatment groups. The average age was 25.5 years (range 17-73 years) in group I and 36.5 years (range 16-64 years) in group II. Most of the injuries occurred during sports activities (n=29, 72.5%), eight patients (20%) have suffered a domestic accident and three accidents occurred at work (7.5%). There were no complications in both treatment groups.

At the primary presentation, the rest pain was scored 5.4 on average in group I, whereas 7.0 in group II. The walking pain was scored with VAS 7.8 and 9.2, respectively. Twenty-five patients, 15 in group I and 11 in group II, complained about violent pain on walking and weightbearing, which is why crutches were prescribed. On average, the crutches were used for 5.9 days in group I, whereas only for 2.9 days in group II, but the difference was not significant.
Table 1: demographic data and outcome parameters

<table>
<thead>
<tr>
<th></th>
<th>Group I (standard care)</th>
<th>Group II (standard care + HA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>male:female ratio</td>
<td>15:5</td>
<td>12:8</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>25.5 (range 17-73)</td>
<td>36.5 (range 16-64)</td>
</tr>
<tr>
<td>pain at primary presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean rest pain (VAS)</td>
<td>5.4</td>
<td>7.0</td>
</tr>
<tr>
<td>mean walking pain (VAS)</td>
<td>7.8</td>
<td>9.2</td>
</tr>
<tr>
<td>use of crutches (number of pts.)</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>mean use of crutches (days)</td>
<td>5.9</td>
<td>2.9</td>
</tr>
<tr>
<td>decrease in pain (regression co-efficient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>walking pain</td>
<td>0.39 ± 0.19</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>rest pain</td>
<td>0.61 ± 0.3</td>
<td>p=0.05</td>
</tr>
<tr>
<td>development of patient global satisfaction (regression co-efficient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean return to work (days)</td>
<td>18 ± 9.9</td>
<td>n.s</td>
</tr>
<tr>
<td>mean return to sport (days)</td>
<td>34 ± 9.2</td>
<td>23 ± 8.9</td>
</tr>
</tbody>
</table>

HA: hyaluronic acid; pts.: patients; n.s.: not significant

The primary criterion was the decrease in walking and weight bearing pain. The chronological development of the mean pain relief in both treatment groups is shown in Figure 1. The mean regression co-efficient was 0.39 ± 0.19 in group I and 0.55 ± 0.27 in group II. The difference was significant (p<0.05). The decrease in rest pain also showed better results in the treatment of group II (Figure 2). The mean regression co-efficient was 0.61 ± 0.3 in group I, and 0.95 ± 0.47 in group II. The difference was also significant (p<0.05). The greatest pain relief was seen in the treatment of group II during the first week regarding both rest pain and walking pain. Similar results were observed concerning the general patient satisfaction. The difference of the regression co-efficient was also significant (p<0.05) in both treatments groups (0.42 ± 0.21 in group I versus 0.59 ± 0.35 in group II). Explorative data concerning the inability to work could be collected from 15 patients in group I (75%) and 11 patients in group II (55%). The mean period to return to work was 18 (± 9.9) days in group I and 14 (± 10.1) days in group II, but the difference was not significant. Fifteen patients in group I (75%) and 16 patients in group II (80%) stated to exercise regularly, i.e. at least 30 minutes twice a week. The period to return to sports activities was 24 (± 9.2) days in group I and 23 (± 8.9) days in group II. The difference was significant (p<0.05). Thirteen out of the 40 patients (32.5%), 8 in group I and 5 in group II, needed analgetic medication. In both treatment groups, only two patients needed analgetics longer than 3 days. Due to the small number of patients statistical analysis was not feasible.

Table 1 gives an overview of the demographic data and the relevant outcome parameters.

**Discussion**

The conservative treatment of acute ankle sprains is generally accepted [3-5, 12-14]. In acute injuries, surgery can be indicated in individual cases of professional athletes or complete ruptures of all ligaments resulting in severe instability. The standard conservative treatment is based on the "RICE"-principles: rest, ice, compression and elevation [3]. The acute, inflammatory phase of ankle sprains associated with local pain and swelling is usually treated with antiphlogistic drugs like NSAID's or cox-II inhibitors. Because of their possible gastrointestinal and cardiac adverse effects and the lack of benefits to the further clinical course of ankle sprains, the search for alternative, safe treatments is reasonable. Hyaluronic acid is reported to have positive effects on the clinical course of osteoarthritis [6], but the potential effect of HA on extra-articular soft tissue or ligamentous pathologies is not well researched. By review of the literature, we found only two prospective studies about the positive effect of HA on ankle sprains [15, 16]. Petrellia et al. [15] randomized 158 athletes with ankle sprains of clinical grade I and II 1:1 for local HA-injection versus placebo-injection. They found benefits concerning...
the decrease in rest pain, as well as in weight bearing and walking pain in the HA treatment group. The results of our study confirmed these findings. But we limited the ankle sprains to acute isolated ruptures of the anterior talofibular ligament and confirmed the diagnosis by ultrasound using the technique of Ernst et al. [7]. In contrast to Petrella et al. [15], we included all injury mechanisms. In our study, about 75% of ankle sprains were the result of sporting accidents: a quarter of the patients suffered from domestic or industrial accidents. We did not differ between walking and weight bearing pain, but the corresponding findings of Petrella et al. [15] justify this equalization.

We could also agree with the statement of Petrella et al. [15] about the more rapid return to sports activities in the HA treatment group. Although we included all injury mechanisms in our study, 75% of the patients declared to exercise at least twice a week. The patients treated with local HA injection could return to sports activities significantly earlier, 11 days on average. Thus, the local HA injection can be an effective additional treatment method in ankle sprains for all athletes, especially for professionals. Potential cause of objection of our study may be the small number of patients and the lack of a real placebo group. Due to ethical reasons, we abstained from local placebo injections. But we think that the primary efficacy criterion of the study, the decrease in walking and weight bearing pain, was reliably represented within each treatment group. Concerning the chronological sequence, we observed the greatest pain relief within the first week after the injection. We also found benefits in the HA treatment group concerning the decrease in rest pain and the improvement of the general patient satisfaction. We used the VAS and not the 5-category scale described by Petrella et al. [15] to define the patient global satisfaction, however, the results are reported to be comparable [8].

One could argue, that the results might be adulterated by the additive NSAID’s medication, but only two patients of each treatment group received NSAID’s for two days or longer. The data concerning the return to work also revealed better results in the HA treatment group (14 versus 18 days), but the difference of the two treatment groups was not significant. Furthermore, the results are considered to be not reliable because we did not differentiate the workload in detail, e.g. sedentary or standing activity.

Ankle sprains can also lead to considerable long-term morbidity. About 30-50% of the patients reported persistent pain or subjective instability [5, 9, 13]. In athletes, local HA injection is also considered to have positive effects in the long term. Petrella et al. [12] reported a significantly lower re-sprain rate, greater patient satisfaction and lower pain level in 123 athletes after 24 months. A statement about the long-term efficacy of HA treatment in ankle sprain was not feasible by our study. However, the positive short-term effects are promising.

**Conclusion**

Additional periarticular injection of hyaluronic acid may influence the clinical course of ankle sprains positively. It leads to a shorter rehabilitation represented by a significantly faster pain relief and return to work and sporting activities. The faster return to sports activities could be crucial, especially in professional athletes. Further studies can be suggested to prove the long-term efficacy. In addition, investigations of the costs and benefits of HA treatment in ankle sprains versus conservative therapy demand attention to return to sports and re-injury rate across the range of different sports in amateur as well as in professional athletes.

**Bibliography**


Correspondence address: PD Dr. R. Wirbel
Department of Trauma-, Hand-, and Reconstructive Surgery,
Verbundkrankenhaus Bernkastel-Wittlich
Koblenzer Str. 91
54516 Wittlich, Germany
Tel 0049-6571-1532310
Fax 0049-6571-1532390
E-mail reiner.wirbel@web.de