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Is thermography the most effective tool to monitor arthritis in rats?

Elif DOGAN*[1], Azizcan SEZER[2]

1. Department of Surgery, Faculty of Veterinary Medicine, Kastamonu University, Kastamonu, Turkey. **2.** Regional Directorate, General Directorate of Nature Conservation and National Parks, Republic of Turkey Ministry of Agriculture and Forestry, Bursa, Turkey. Doğan E.: ORCID: 0000-0002-3321-8116, Sezer, A.: ORCID: 0000-0003-4604-0705.

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ABSTRACT

In this study, it was aimed to compare the effect of clinical, radiological, and thermographic methods on the diagnosis and prognosis in experimentally rats with arthritis. A total of 24 rats were divided into 2 groups, each consisting of 12 rats. Arthritis was formed by administering 0.1 ml of FCA solution to the left-back extremities of the rats. The first group was called the control group. Cephalexin (60 mg/kg) and Diclofenac Sodium (1mg/kg) were applied to the second group to be the treatment group. From day 1 of the experiment, clinical evaluation and body weight measurements were performed every day. On the 7th, 14th, 21st, 28th days of the experiment, paw edema, radiographic, thermographic measurements were performed. While typical arthritis clinical findings obtain after FCA administration, no statistically significant difference was found when analyzing the changes of body weight measurements and paw edema measurements according to groups and time. The difference in the mean of the thermographic measurements of the arthritis-forming claws was statistically significant. Radiographically, degenerations in the joints and bones were found in the control group compared to the more in the treatment group. As a result, it was concluded that thermography can be a good alternative to clinical findings and radiography in the follow -up of arthritis.

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Introduction

Arthritis is the inflammation of one or more of the structures that make up the joint. In cases of arthritis, the joint cartilages lose their clarity while their color becomes darker or lighter. As long as joint movements continue, abrasions, which can vary from microscopic measurements to a few mm, are formed on the cartilage surface (Samsar and Akın, 2003). Clinical, radiological, and synovial fluid examinations are routinely used for diagnosis of arthritis (Gökhan and Öztürk, 2016). The most important criterion of joint radiography is the visualization of the joint space. The width and stenosis of the joint space may differ with the movement or position of the joint (Sarıerler and Alkan, 2002). While no finding can be determined by direct radiography in acute arthritis, the earliest finding in acute septic arthritis is joint effusion (Gökhan and Öztürk, 2016). In septic arthritis, the first radiographic findings are determined 24 hours after the disease occurs and begin to occur within 5-10 days at the earliest. There is an increase in joint volume during this period, but the radiographic data are not clear (Bumin et al., 2001). Radiographic findings are obtained after 4 -5 weeks. At this stage, thickening of the joint capsule and increase in opacity, lytic changes in the subchondral bone, periarticular osteopenia, alignment disorders in the intercarpal bones, and bone erosions

*Corresponding Author: Elif Doğan
E-mail: elifdogan@kastamonu.edu.tr

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in the joint cartilage. Besides, osteomyelitis and soft tissue abscesses can occur. In the last stage, destruction is observed in the bone and joint (Bumin et al., 2001; Chew, 2010).

The thermographic examination is a non-invasive method used for diagnostic purposes in veterinary medicine (Hovinen et al., 2008). It is known that damaged tissues and organs are at different temperatures than normal. Diseased areas can be identified by detecting the heat spread that occurs. The infrared thermal camera determines the temperature and infrared radiation created by the blood circulation in the capillaries in the skin. Thanks to the thermographic devices, which are advanced technological products, the information about the temperature that occurs on the skin of the animals are transferred to the digital environment in the form of color images (Düzgün and Or, 2009). This technique is used to determine the physiological and functional disorders that occur in tissues, and to examine the changes before, during, and after the treatment of a diagnosed disease. It is very effective in early diagnosis as even very low-temperature differences can be detected (Laughmiller et al., 2001; Düzgün and Or, 2009).

In this study, it was aimed to compare clinical findings, radiography, and thermographic findings in arthritis. Besides, it was hypothesized that thermography could be as effective as clinical findings and radiography in the diagnosis and prognosis of arthritis.

Material and methods

This study was carried out within the framework of the experimental protocol approved by Atatürk University Animal Experiments Local Ethics Committee (HADYEK) (2016/136). The animal material of the study consisted of 24 male Sprague Dawley rats, 10 months of age, weighing 408-504 g. 24 rats were divided into 2 groups as 12 rats in each group. To induce arthritis in the hind left paws of all rats, 0.1 ml of FCA (Freund's Complete Adjuvant, Sigma, USA) solution was administered subcutaneously at four points circumferentially (Wang et al., 2018). Clinical signs of arthritis were formed in all rats after a three-day waiting period. At the next stage, while the treatment protocol was not applied to the control group, the rats in the treatment group were given cephalexin (60 mg/kg, SEF, 250 mg/5 ml Mustafa Nevzat, Turkey) and diclofenac sodium (1 mg/kg, Diclofenac Sodium, Sigma) by gavage 5 times a week.

Clinical evaluation: At the 7th, 14th, 21st, 28th days after arthritis has been experimentally established. Swelling in the left paws and all extremities, skin temperature and color changes, the presence and severity of lameness during walking, the presence of reduced mobility, and the presence of open wounds, abscesses and fistulas in the area were noted. On the specified days, paw edema was measured by filling the test tube with water and calculating the amount of overflowing water by dipping the paw (Özbek and Öztürk, 2003) for all rats.

Thermographic measurements: Thermographic measurements were made on the 7th, 14th, 21st, and 28th days from the dorsal, medial, lateral, and plantar sides of the left paws. (IR Flexcam-S®, USA). Measurements were carried out at room temperature without anesthesia and made from the distance received the clearest image without the use of artificial light. During the measurement, care was taken that the paws were not wet.

Radiographic measurements: Radiographs of rats under general anesthesia (IM, 8 mg/kg xylazine hidroklorür, Rompun 2%, Bayer, Turkey, 30 mg/kg ketamine hidroklorür, Ketasol 10%, İnterhas, Austria) were taken on the 7th, 14th, 21st, and 28th days. Radiographic images (Meditronics 3L 103, Japan) were taken with the paws in the anteroposterior position.

Statistical analysis: Descriptive data (body weight and paw edema measurements) were analyzed by the mean procedure. Colmogorov-Smirnov method was used for the normality test. Two-way analysis of variance with repeated measurements method was used in the analysis of thermographic data. Dependent variables (thermographic data); group (control and treatment) and time (days) were modeled based on fixed variables. Main effect and interaction effect significance ($p < 0.05$) and group/ subgroup means are presented with standard error values. SPSS version 16.0 package program (SPSS, Chicago, ILL) was used for data analysis.

Results

Clinical evaluation findings: On the 14th day of the experiment, 2 rats in the control group had a fistula on the dorsal side of the paw. On the 16th day, a fistula with pus flowing mixed with blood was detected on the plantar side of the paw in 1 rat in the treatment group. When the statistical analyzes of the body weight measurements were made until the experimental protocol was completed, it was determined that the body weights did not change significantly according to time and groups. The average paw edema measurements during the experiment were calculated as 2.37 (±0,149) ml in the treatment group and 3.86 (±0,121) ml in the control group. When the changes in the measurements taken were analyzed by groups and time, no statistically significant difference was found.

Thermographic findings: Thermographic measurements taken from the dorsal, medial, lateral, and plantar sides in the treatment and control groups on the 7th, 14th, 21st, and 28th days are given in Table 1. When the temperatures taken from the arthritic paws were evaluated according to the groups and time, no statistical difference was found. However, when the average temperature was evaluated until the end of the experiment, a significant difference was found. It was determined that the highest mean measurement was in the plantar side in the control group (Table 2). The biggest difference between the two groups was in the mean temperatures taken from the medial side (Table 2, Figure 1).

Table 1. Thermographic measurements taken from left paws.

Side	Days	Control (°)	Treatment (°)
Dorsal	7	36.77 ± 0.34	34.58 ± 1.30
	14	35.22 ± 0.30	34.52 ± 0.51
	21	32.32 ± 0.50	31.52 ± 0.92
	28	31.62 ± 1.70	29.57 ± 0.41
		NS	NS
Medial	7	36.94 ± 0.35	34.61 ± 1.29
	14	35.02 ± 0.33	34.16 ± 0.53
	21	32.60 ± 0.40	31.90 ± 0.67
	28	31.22 ± 1.26	29.60 ± 0.42
		NS	NS
Lateral	7	36.77 ± 0.25	34.51 ± 1.31
	14	34.75 ± 0.50	34.70 ± 0.52
	21	32.45 ± 0.31	31.22 ± 0.80
	28	30.80 ± 1.09	30.00 ± 0.32
		NS	NS
Plantar	7	37.05 ± 0.34	34.65 ± 1.30
	14	35.43 ± 0.44	34.88 ± 0.61
	21	32.40 ± 0.54	31.78 ± 0.65
	28	31.27 ± 1.57	29.83 ± 0.43
		NS	NS

NS = nonsignificant

Radiographic findings: In the radiographic images taken on the seventh day, an increase was observed in the metatarsophalangeal joint distances in the left extremities of the animals in both groups. On the 14th day of the experiment, it was determined that the metatarsophalangeal joint spaces were closed in the rats in the control group, but the joint space was normal in the rats in the treatment group. The phalanx and tarsal bones of the rats in the control group had degeneration on the 21st day of the experiment. Osteophytic formations in phalanges and tibiotarsal joint degenerations were observed in one rat. (Figure 2A). Metatarsophalangeal and tibiotarsal joint degenerations were seen in the treatment group. (Figure 2B). In the radiographs taken on the 28th day, it was seen that the rats in the treatment group had less bone and joint degeneration than the rats in the control group. In the radiographs of all rats in the control group, degenerations in all phalanges were determined. Fractures were seen in the 2nd, 3rd, and 4th phalanges of one rat. (Figure 2C). In all rats, it was determined that the joint spaces in the metatarsophalangeal joints were closed, joint integrity was impaired and tarsal joint alignment was changed. (Figure 2D).

Table 2. Thermographic measurements taken from different sides according to groups.

Side	Control (°)	Treatment (°)	*P* values
Dorsal	33.9 ± 0.40	32.5 ± 0.36	0.017
Medial	33.9 ± 0.32	32.5 ± 0.38	0.009
Lateral	33.6 ± 0.33	32.6 ± 0.39	0.043
Plantar	34.0 ± 0.33	32.7 ± 0.40	0.022

Discussion

Arthritis is a disease that is very common in animals and takes time to treat. For this reason, many experimental arthritis studies have been conducted to date (Saricaoglu et al., 2008; Cenesiz et al., 2012; Kerimoğlu et al., 2017). In these studies, generally adult rats were used to create adjuvant arthritis (Gertel et al., 2015). In accordance with previous reports, experimental arthritis was created in adult rats and the disease was followed up for 28 days.

In the clinical examination of arthritis, lameness is inevitable due to swelling and pain. On palpation of the area, fistulization, and pus discharge are described in most cases with an increase in temperature (Rao et al., 2020). In our study, it was determined that temperature increase and bloating occurred on the 3rd day in accordance with previous reports. On the 14th day of the experiment, fistulas with a purulent discharge mixed with blood were detected on the dorsal side of the paw in two rats in the control group and on the plantar side of the paw in one rat in the treatment group. In the last week of the experimental protocol, it was observed that the fistulization in the

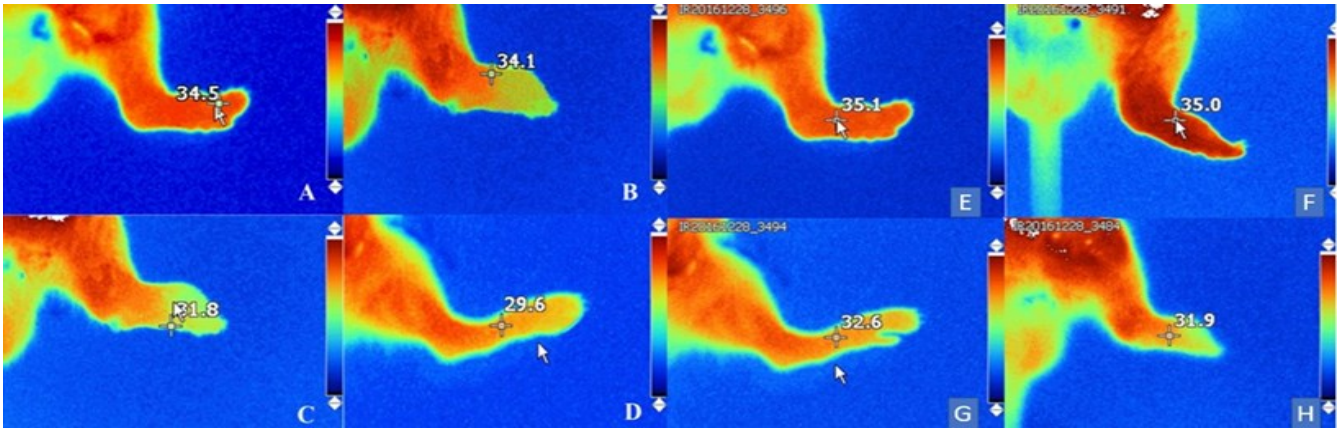

Figure 1: Thermographic images taken from the medial side of rats in the treatment and control groups. Treatment group (A; 7th day, B; 14th day, C; 21st day, D; 28th day), Control group (E; 7th day, F; 14th day, G; 21st day, H; 28th day).

rats in the treatment group decreased and the discharge disappeared. It was observed that the fistula formed in the treatment group closed more quickly due to the drugs used.

Disease symptoms have been studied for a long time. It has been mentioned that the temperature increase in the skin in ancient Egypt is an indicator of diseases. Although skin temperature can be affected by many factors, it is a known fact that it may be an indicator of inflammatory disease (Borojevi et al., 2011). Clinical findings in which skin temperature is also controlled, radiological findings, and laboratory tests are used for diagnosis in cases of arthritis (Naredo et al., 2005). The effectiveness of the use of thermography has begun to be investigated in both animal models and humans for diagnostic purposes (Jiang et al., 2005; Düzgün and Or, 2009).

Inflammatory lesions in the joints are characterized by an increase in temperature with increased vascularization in the inflamed tissue (Cuevas et al., 2015). Since joint damage may occur in the early stages of the disease, the use of a thermal camera becomes important (Düzgün and Or, 2009). To elaborate the thermographic findings, we made measurements from four different points: dorsal, medial, lateral, and plantar of the paw. It was determined that the temperature increases at four points in the rats in the treatment group were almost the same (dorsal 32.5 °C, medial 32.5 °C, lateral 32.6 ° C and plantar 32.7 °C). In the control group, the temperature values on the dorsal, medial, and lateral sides were very close to each other (dorsal 33.9 °C, medial 33.9 °C and lateral 33.6 °C), while the temperature on the plantar surface was higher (34 ° C). It was concluded that the increase in temperature taken from the plantar side resulted from the fact that the paws of the rats stepped on the ground with the plantar side and the blood circulation increased due to the trauma during the press. This situation may be misinterpreted in the pathogenesis of the disease, especially in cases where treatment is delayed, if immobility is not achieved, as it will lead to an increase in local temperature. It was concluded that measurements taken from the dorsal, medial, and lateral sides would be more advantageous than the plantar side clinically. Although there was no significant change in body weight and paw edema measurements until the end of the experiment in our study, a significant difference was found when the thermographic measurements were evaluated. We thought that even in cases where clinical symptoms did not fully occur, thermography could yield results for the diagnosis of the clinician. Therefore, the determination of regional temperature should be considered as an important parameter in arthritis cases.

In the study performed on knee joints with osteoarthritis in humans, thermographic and radiological follow-up was performed and the thermographic temperatures obtained correlated with the severity of the radiological findings (Denoble et al., 2010). In arthritis cases when the direct radiographic examination is performed, an increase in joint spaces, osteomyelitis, porosity and subluxations on the surfaces of the bones forming the joint can be determined (Öztuna, 2010). In our study where we experimentally created arthritis, an increase in metatarsophalangeal joint distances in the left extremities of rats in both groups were detected on the seventh day, On the 14th day, it was found that the joint gaps were closed especially in the rats in the control group. In our radiographic findings on the seventh day, no findings emerging in chronic cases such as degeneration or bone growth on the bone surfaces were observed besides the increase in joint space. We thought that this was because the

Figure 2: Radiographs taken on the 21st and 28th day. Degeneration in the tibiotarsal joint on day 21 (A, Arrow 1) and osteophytic formations in the phalanges (A, Arrow 2), Degeneration in the tibiotarsal joint of a rat in the treatment group on the 21st day (B). It was determined that two rats in the control group had fractures in the phalanges on the 28th day (C) and another rat had tibiotarsal joint degenerations (D).

destructions in the joint tissue had not yet progressed. As stated in the study (Örgüç, 2014), the joint distance narrowing that occurs with the progression of the destruction process and the formation of fibrosis is among the findings of the 14th day of our study. Considering the 14 days of the experimental protocol, the initial period of arthritis is in line with the literature data (Moskowitz and Holderbaum, 2001). On the 7th day radiographically, the joint space was enlarged due to effusion, Then, due to cartilage destruction, erosions in the bone regions, and symmetrical narrowing in the joint space were detected radiographically, especially in the control group, in the second week of our study. Arthritis is considered a disease that can cause rapid destruction of joints and bones (Yanık et al., 2007). It is a chronic disease that is noticed with the emergence of edema at the earliest 48 hours after its formation (Nipate and Bhandarkar, 2020) and does not cause bone destruction until at least 1/3 of the bone matrix is affected (Öktem et al., 2016). It has been reported that the radiographic findings became clear a few weeks after the onset of the disease, and could not create data to determine the prognosis in the previous period (Yurdakul and Sarıtaş, 2013). In accordance with the literature, it is very important to use radiographic and other imaging methods together with the clinical examination of arthritis with bone destruction in terms of determining the prognosis. According to a published literatüre (Nipate and Bhandarkar, 2020), The narrowing of the joint spaces indicates the progression of the disease and there is little correlation with the clinical symptoms during these periods. On the 14th day of the experimental protocol, we determined that the metatarsophalangeal joint gaps were closed in all rats in the control group. Our study findings are consistent with this study (Nipate and Bhandarkar, 2020). At the same time, it was concluded that imaging methods have a very important place in terms of diagnosis and prognosis in arthritis cases due to the low correlation with clinical symptoms.

Conclusion

As a result, the significant increase in local temperature in arthritis cases, which can be seen in all animal species and may progress with bone destruction, has led to the use of thermography, which is one of the imaging methods. Especially in cases of acute arthritis, while bone and joint destruction cannot be determined exactly on the radiography, determining the temperature increase in the thermographic allows the diagnosis of the disease to be made very early. According to our study findings, we recommend performing a routine thermography screening and suspecting the presence of a lesion when a temperature increase of even one degree is detected. In arthritis cases where the treatment is more difficult with the late diagnosis, the advantage of thermography is that it can be diagnosed with thermographic temperature increase before the radiological symptoms appear. Another advantage of thermography is that the prognosis can be determined more easily by interpreting temperature changes in the tissue after the diagnosis of the disease and comparing it with healthy tissue.

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