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Original Article ORTHOPEDICS & TRAUMATOLOGY

Comparison of linear versus macrocyclic gadolinium chelates in rat skeletal muscle

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ABSTRACT

OBJECTIVE: We investigated the effects on skeletal muscle of gadolinium based linear and macrocyclic radiocontrast agents applied at experimental intervals using histopathological methods.

METHODS: Thirty-two male Sprague–Dawley rats were included in the study for histopathological analysis. No procedure was performed on the healthy control group. The sham group received 0.1 ml/kg intravenous (IV) saline solution through the tail vein 4 times weekly for 5 weeks. The gadodiamide group received total 2 mmol/kg IV gadodiamide through the tail vein 4 times weekly for 5 weeks. The gadoteric-acid group received 2 mmol/kg IV gadoteric acid through the tail vein 4 times weekly for 5 weeks.

RESULTS: We determined no marked apoptotic myofibrils associated withcaspase-3 expression in these two groups. Furthermore, no calcineurin expression was observed in myofibrils in the two groups. However, quantitative analyses revealed a decrease in muscle-fiber area in the gadodiamide and gadoteric-acid groups compared to the control group (Respectively; p=0.001 and p=0.017).

CONCLUSION: In our experimental study, linear and macrocyclic GBCAs applied at repeated doses played no role in myofibril damage induced by caspase-3 and calcineurin – nuclear factor of activated T-cells in skeletal muscle tissue.

Keywords: Calcineurin; caspase-3; gadodiamide; gadoteric acid; skeletal muscle.

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The masses are common in the muscle, and the distinction between benign and malign muscle lesions is important [1]. Like these lesions, magnetic resonance imaging (MRI) is used for the diagnosis of the masses that settled in the pelvis [1, 2]. Gadolinium(Gd)-based agents are radiocontrast substances frequently used in MRI [3]. However, the use of Gd alone leads to undesirable problems, and greater safety is achieved in the form of chelates [4, 5]. Two Gd-based agents that are frequently used in this context are linear gadodiamide and macrocyclic gadoteric acid [6]. Even though the macrocyclic and linear agents are not referred to as toxic in the

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literature in comparison to other contrast agents, some studies have shown that they can accumulate and result in toxicity in organs and tissues such as the kidneys [4], brain [4, 5], testis[7], and liver [8].

Skeletal muscle, which represents a significant part of the body and which, together with bone, gives the body its shape, can be affected by aging, various infections, and a range of pathologies including inflammatory diseases in normal individuals; these can cause severe muscle loss [9]. The previous studies have shown that radiocontrast materials can cause renal toxicity [10, 11]. However, there have been insufficient studies of the potential effects of the systematic application of these agents on skeletal muscle. In addition, Brown et al. [12] reported encountering cardiac arrest resulting from the use of radiocontrast materials at short intervals. Skeletal and cardiac muscles resemble each other in many ways, both having a myofibril structure [13, 14]. This similarity suggests that these agents may be capable of causing deleterious effects on skeletal muscle in association with frequent use.

Studies of Gd-based agents have reported that they cause apoptosis in the cell through an unknown mechanism [8, 15, 16]. The previous studies have revealed that caspase-3, an important apoptotic protein, exhibits antiproliferative effects by stimulating intracellular signaling pathways [17, 18]. Research has also shown that intracellular calcium causes cell damage by means of Ca^{+2}-dependent calcineurin activation [19].

We, therefore, investigated the effects on skeletal muscle of Gd-based linear and macrocyclic agents applied at experimental intervals using histopathological and immunohistochemical (IHC) methods for the purpose of guiding future studies.

Highlight key points

- There aren' t significant histopathological effects of the linear and macrocyclic GBCAs.
- Gadolinium-based agents don' t accumulate in skeletal muscle when used repeatedly and can' t cause deleterious effects.
- There is an increase in caspase-3 expression in myofibrils caused by linear and macrocyclic GBCAs.

MATERIALS AND METHODS

Animal Studies

Thirty-two male Sprague–Dawley rats weighing 280±15 g were included in the study for histopathological analysis. All animals were treated in line with the principles of laboratory-animal care formulated by the Use and Care of Laboratory Animals Guideline published by the National Health Research Council and National Laboratories and approved by the Local Ethical Committee. Before the study and during the experiment, the rats were kept under normal temperature conditions at 22±2°C and at 55–60% humidity in standard plastic cages with sawdust flooring under controlled lighting (12: 12-h light/dark cycle) and were allowed ad libitum access to standard rat chow and tap water [20]. Animal experiments and procedures were performed in accordance with the national guidelines for the use and care of laboratory animals. The study protocol was approved by the Local Animal-Care Committee of University, (2016/47- 22.12.2016).

The animals were divided into four equal groups. No procedures were applied to Group 1, the healthy control group. The sham group (Group 2) received 0.1 ml/kg intravenous (IV) saline solution through the tail vein 4 times weekly for 5 weeks. The gadodiamide group (Group 3) received total 2 mmol/kg (total: 0.1 mmol/kgx20 days=2 mmol/kg) IV gadodiamide (Omniscan, Opakim, Istanbul, Turkiye) through the tail vein 4 times weekly for 5 weeks [4, 7, 8, 21]. The gadoteric-acid group (Group 4) received 2 mmol/kg (total: 0.1 mmol/kgx20 days=2 mmol/kg) gadoteric acid (Dotarem, Guerbet, Istanbul, Turkiye) through the tail vein 4 times weekly for 5 weeks [4, 8, 15, 21]. With the exception of Group 1, drug administration was IV for 5 weeks through the tail vein using a 24-gauge catheter (Terumo, Japan). Ketamine hydrochloride (50 mg/kg) (Ketalar, 100 mg/10 ml, Pfizer Pharmaceuticals, Istanbul, Turkiye) together with the sedative xylazine hydrochloride (10 mg/kg) (Rompun, 2%, Bayer Turkiye Pharmaceuticals, Istanbul, Turkiye) was used for anesthesia by intraperitoneal administration. At the end of the experiment, rats were given terminal anesthesia skeletal muscle specimens that were removed in the right femoral muscle, fixed in 10% formalin for microscopic examination and histopathological analysis, and placed in storage.

Histopathological Analysis

Following fixation in 10% formalin, skeletal muscle specimens were subjected to routine histological procedures and embedded in paraffin blocks. Sections 3–4 μm in thickness were taken from these blocks using a microtome (Leica, RM2525, Darmstadt, Germany).

The skeletal muscle slides were then stained with Harris hematoxylin (Merck, Darmstadt, Germany) and Eosin G (Merck, Darmstadt, Germany). During histological analysis, sections were evaluated by two blinded histopathologists (TM) using a light microscope (BX51, Olympus Corp., Japan). One TM had 8 years' experience in the field and the other (LT) 10 years.

Immunohistochemistry Analysis

Skeletal muscle-tissue sections were incubated with caspase-3 antibody (rabbit polyclonal antibody, ab2302, Abcam, UK) and anti-calcineurin a antibody (rabbit polyclonal antibody, ab71149, Abcam, UK) and then washed with phosphate buffer solution (PBS) and incubated in anti-digoxigenin-peroxidase. The sections were subsequently incubated with 0.06% 3,3-diamino benzidine tetrahydrochloride in PBS. In the final step, the sections were counter-stained with Harris hematoxylin.

Semi-Quantitative Analysis

Histopathological assessments of the skeletal muscle sections by light microscopy were performed, as shown in Table 1 in the light of the literature [22–24]. Atrophic myofibrils were scored by two blinded TM (TM and LT), as shown in Table 1. The histopathologists were not present during the experimental procedures or the histological preparation of the skeletal muscle specimens.

Quantitative Analysis

Skeletal muscle areas (μm^2) were calculated using the Olympus DP2-BSW (Ver. 2.1 to Ver. 2.2, Build 6212, Tokyo, Japan) software system. This system consists of a camera (Olympus DP20) attached to a light microscope (Leica DM 6200, Germany) and a computer with a software system. All group sections stained with H&E were placed on the microscope tray. The sectional boundaries of each specimen were determined by two blinded histologists (TM and LT).

Statistical Analysis

Skeletal–muscle-area data were calculated on SPSS 18.00 software (IBM Corp., New York, USA). Data were expressed as a mean±standard deviation, and analyses were performed using the Tukey test. Atrophic-muscle score data were expressed as a Median±standard deviation, and analyses were performed using the Kruskal–Wallis test. $P<0.05$ was regarded as significant.

Table 1. Atrophic myofibril grade

Grade (%)	Atrophy myofibril
None	<5
1	5–25
2	25–50
3	More than 50

RESULTS

Histopathological Results

Skeletal muscle from the control group exhibited a normal histological structure at light-microscopic examination (Fig. 1A, B). Saline-group skeletal muscle tissue exhibited a similarly typical structure (Fig. 1C, D). In the gadodiamide group, we observed no pathological findings other than a few atrophic myofibrils ($p=0.065$; Table 2) (Fig. 1E, F). Similarly, we discovered no pathological change in sections from the gadoteric-acid group, apart from a few atrophic myofibrils ($p=0.0392$; Table 2, Fig. 1G, H). We determined that there was no significant histopathological difference between the gadodiamide and gadoteric-acid groups (Fig. 1E, H).

IHC Results

We observed no caspase-3 and calcineurin expression in the control and saline groups (Fig. 2A, B; Fig. 3A, B). We also discovered no marked apoptotic myofibrils in the gadodiamide or gadoteric groups (Fig. 2C, D). No calcineurin expression was observed in myofibrils in the gadodiamide and gadoteric-acid groups (Fig. 3C, D).

Quantitative-Analysis Results

Mean skeletal muscle-fiber areas were similar in the control and saline groups ($p>0.05$; Table 3). In contrast, mean skeletal muscle-fiber area decreased significantly in the gadodiamide group compared to the control group ($p=0.001$; Table 3). Similarly, skeletal muscle-fibers area was significantly lower in the gadoteric-acid group than in the control group ($p=0.017$; Table 3). We determined that there was no significant difference in skeletal muscle-fiber areas between the gadodiamide and gadoteric-acid groups (Table 3).

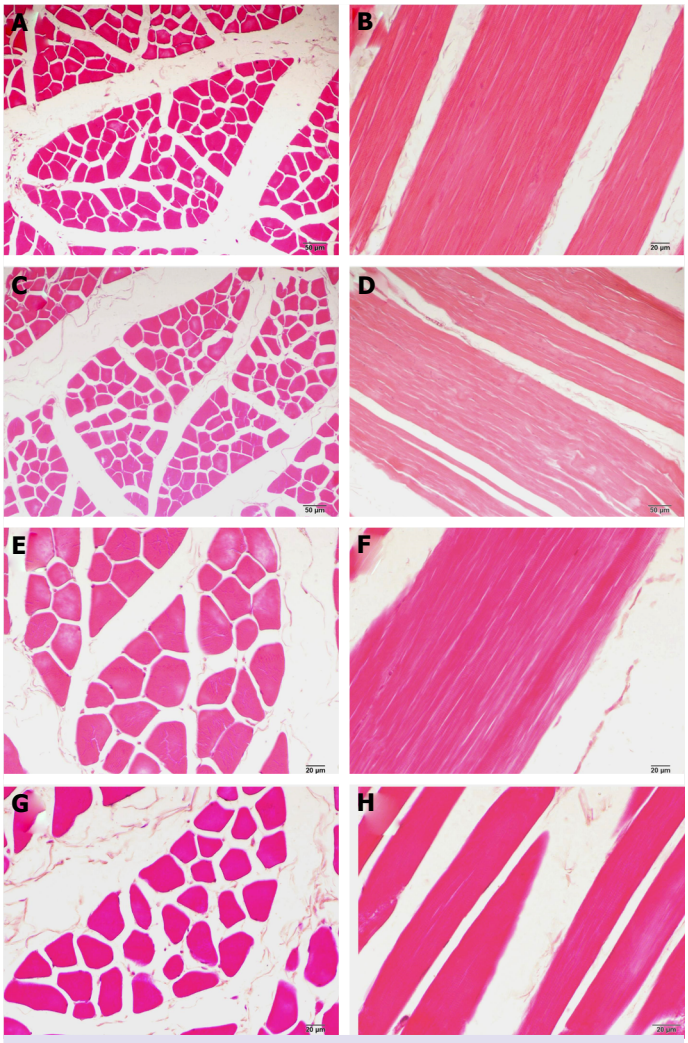

FIGURE 1. Representative light microscopic image of skeletal muscle tissuelight microscopic image of skeletal muscle tissue H&E staining. **(A, B)** Control group; healthy morphological structures of the skeletal muscle tissue. **(C, D)** Saline group; normal morphological structures of the skeletal muscle tissue. **(E, F)** Gadodiamide group: No pathologywasobserved. **(G, H)** Gadoteric acid group: No pathology was observed.

TABLE 2. Atrophic myofibril score data

Group	Score (Median±SD)
Control	0.00±0.35
Saline	0.00±0.44
Gadodiamide	1.00±0.52*
Gadotericacid	0.00±0.52**

*: P=0.065, control group versus to Gadodiamide group; **: P=0.392, control group versus to Gadoteric acid group; SD: Standard deviation.

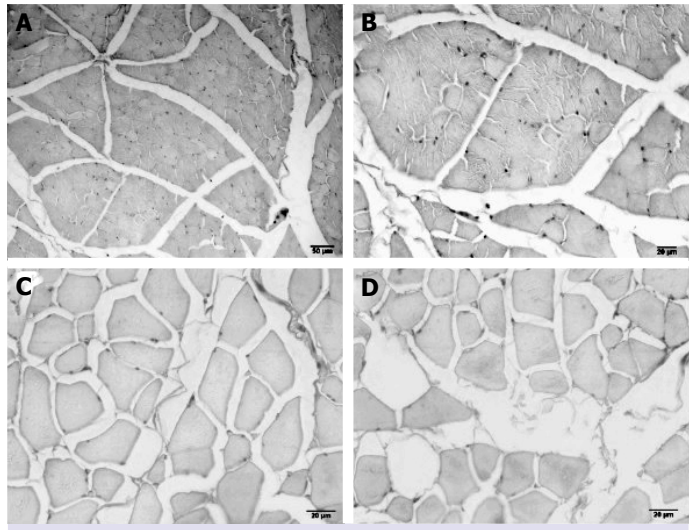

FIGURE 2. Representative light microscopy image of IHC staining Caspase-3. **(A)** Control Group; **(B)** Saline Group; **(C)** Gadodiamide Group; **(D)** Gadoteric acid Group.

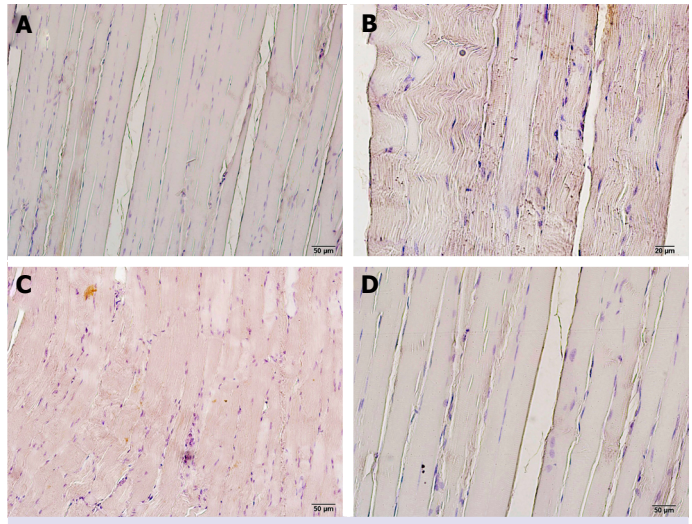

FIGURE 3. Representative light microscopy image of IHC staining. Calcineurin. **(A)** Control Group; **(B)** Saline group; **(C)** Gadodiamide group; **(D)** Gadoteric acid group.

DISCUSSION

Gadolinium-based substances are frequently used in MRI due to their considerable contributions to imaging and the fact that they are reliable when used in appropriate doses [25, 26]. However, recent studies have shown that these gadolinium-based agents accumulate in several tissues when used at short intervals and cause deleterious effects through a damage mechanism that

Table 3. Skeletal muscle area (μm²) data

Group	Area (μm²) (Mean±SD)
Control	1483.63±179.81
Saline	1443.63±215.10
Gadodiamide	1105.3116±53.38*
Gadotericacid	1201.32±206.36**

*: P=0.001, control group versus to Gadodiamide group; **: P=0.017, control group versus to Gadoteric acid group; SD: Standard deviation.

is not yet fully understood [27, 28]. In their study of the toxicity mechanism caused in tissues by gadolinium-based contrast agents (GBCAs), Hanana et al. [29], similarly, reported that GBCAs make no contribution to the production of free-oxygen radicals, but that their damage mechanism is related to their role in the induction of inflammatory response. The previous studies have reported that pro-inflammatory cytokines induce apoptosis [30, 31].

Caspase-3 is a protein that plays an irreversible role in apoptosis and is used as a marker of apoptosis [32, 33]. Xia et al. [34] showed that GBCAs cause apoptosis by giving rise to caspase-3 activation in neurons. In contrast, Kishta et al. [35] reported that gadolinium reduced caspase-3 expression. In our study, the increase in caspase-3 expression in myofibrils caused by linear and macrocyclic GBCAs but was not a significant statistical difference.

The second biomarker examined in this study was calcineurin. This is a phosphatase enzyme shown in several previous studies to play a role in the differentiation of several tissues, including skeletal muscle [24, 36]. It has been shown to cause hypertrophy in skeletal muscle and changes in myofibrils through the calcineurin/NF-ATc1 signaling pathway. Calcineurin also controls muscle-fiber length through this pathway [37, 38]. In our research, we determined that linear and macrocyclic agents do not induce calcineurin expression in skeletal muscle myofibrils. In addition, when we examined mean fiber areas, we determined a significant difference in the application groups. From that perspective, this decrease may perhaps be due to other paths and pathways than calcineurin-nuclear factor of activated T-cells (NFAT) signaling. This issue can be the subject of other studies.

In another clinical study, Ranga et al. [39] found that although GBCAs can be completely eliminated from the body, radiocontrast material entering the central nervous system can accumulate there. From that perspective, it may be suspected that Gd-based substances may also frequently accumulate in skeletal muscle in both normal individuals and in those with underlying disease. We discovered a significant decrease in skeletal muscle-fiber areas compared with the control group. This suggests that extended use of this substance may cause negative effects in skeletal muscle.

The present research is a preliminary study and has a number of limitations. Our apoptosis findings need to be supported by TUNEL and intracellular calcium-level measurements. In addition, linear and macrocyclic GBCA accumulation in skeletal tissue also needs to be supported by measurement.

Conclusion

This study has shown that repeated administration of microcyclic and linear GBCAs does not result in myofibrillar degeneration through caspase-3 and calcineurin/NFAT activation. However, the average myofibrillar mass was reduced, the cause of which is unclear. Future studies will illuminate what lies behind this observation.

Ethics Committee Approval: The Recep Tayyip Erdogan University Clinical Research Ethics Committee granted approval for this study (date: 22.12.2016, number: 2016/47).

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