의학 석사 학위논문

Monitoring tumor response to the vascular disrupting agent CKD-516 in a rabbit VX2 intramuscular tumor model using PET/MRI: Evaluating vascular and metabolic parameter simultaneously

토끼종양모델에서
양전자단층촬영-자기공명영상(PET/MRI)을
이용한 혈관차단제 CKD-516 에 대한 반응
평가: 혈류 및 대사 파라미터의 동시 평가

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토끼종양모델에서 양전자단층촬영-자기공명영상(PET/MRI)을 이용한 혈관차단제 CKD-516에 대한 반응 평가: 혈류 및 대사 파라미터의 동시 평가

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Abstract

Monitoring tumor response to the vascular disrupting agent CKD-516 in a rabbit VX2 intramuscular tumor model using PET/MRI: Evaluating vascular and metabolic parameter simultaneously

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Purpose: To evaluate the changes of vascular and metabolic parameters in rabbit VX2 intramuscular tumors using PET/MRI following administration of CKD-516

Materials and Methods: With institutional Animal Care and Use Committee approval, 18 VX2 carcinoma tumors implanted in bilateral back muscles of 9 rabbits were evaluated. Serial PET/MRI were performed before, 4 hours and 1-week after vascular disrupting agent,

CKD-516 (treated group, n=10) or saline (control group, n=8) administration. Vascular parameters including the volume transfer coefficient (K^{trans}) and the initial area under the gadolinium concentration-time curve until 60 seconds (iAUC), as well as metabolic parameters including maximum and average standardized uptake value (SUVmax and SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were measured. PET/MRI-derived parameters and their interval changes were compared between the treated and control group by using the linear mixed model. Each parameter within each group was also compared by using the linear mixed model.

Results: Changes of K^{trans} and iAUC in the treated group were significantly larger compared with those in the control group at 4-hour follow-up (mean, -39.91% vs. -6.04%, P = 0.018; and -49.71% vs. +6.23%, P = 0.013). Change of MTV in the treated group was significantly smaller compared with that in the control group at 1-week follow-up (mean, +118.34% vs. +208.87%, P = 0.044). Serial measurements in treated group revealed that K^{trans} and iAUC decreased at 4-hour follow-up ($P < 0.001$, respectively) and partially recovered at 1-week follow-up (P = 0.001 and 0.024, respectively). MTV increased at 4-hour follow-up (P = 0.038) and further increased at 1-week follow-up ($P < 0.001$).

Conclusion: PET/MRI is able to monitor the changes of vascular and metabolic parameters at different time points simultaneously, and confirmed that vascular changes precede the metabolic changes by VDA, CKD-516.

Keywords: PET/MRI, Vascular disrupting agent, Treatment response, Vascular parameter, Metabolic parameter

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Introduction

Supply of oxygen and nutrients via the surrounding vasculature is essential for tumor growth. Therefore, tumor vasculature has been a main target for cancer treatment. Apart from antiangiogenic drugs which compromise the formation of new blood vessels, vascular disrupting agents (VDAs) target the established tumor vasculature and cause shutdown of blood flow, leading to subsequent tumor ischemia and necrosis (1). Because of its' cytostatic nature, conventional assessment of tumor response based on reduction in tumor size, using Response Evaluation Criteria in Solid Tumors (2) may not be adequate or prompt because of the considerable delayed time it takes to determine the clinical effectiveness (3). Physiologic or metabolic responses occur soon after the start of anticancer therapy, although clinical responses are slow. Therefore, functional molecular imaging techniques that depict physiologic and cellular processes within tumors such as vascularity or metabolism have been emphasized (4). Depiction of these post-therapeutic event earlier than clinical endpoint is helpful for choosing the right treatment strategy, preventing unnecessary long treatment courses with their inherent adverse events as well as deciding whether to go or no go in the development of anticancer pharmaceuticals (5, 6). Several imaging technique have been investigated to assess angiogenic vasculature and monitor efficacy of vascular targeting agents, noninvasively (3). Majority of them were studied with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameters for assessing therapeutic effect of vascular targeting agents (3, 6-10). Also, only a

few previous studies were performed with [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) for assessing metabolic change after the therapeutic effect of anti-vascular drugs (11-13). However, to our knowledge, until now, no studies dealing with post-treatment changes after VDA have been performed yet with the novel imaging modality PET/MRI, which can obtain multiparametric information simultaneously.

CKD-516, a newly developed small molecule drug, is an tubulin polymerization inhibitor that has dual action mechanism of (a) rapid disruption of pre-existing tumor vasculature, resulting in hypoxia and necrosis, and (b) arresting the cell cycle, resulting in apoptosis (14).

Therefore, the aim of this study is to determine whether the CKD-516 produces a significant change in vascular and metabolic parameters in PET/MRI.

MATERIALS AND METHODS

Animal model

This study was approved by the Animal Care and Use Committee of Seoul National University Hospital. Sixteen male New Zealand White rabbits weighing 3.0 - 3.5 kg were used. For each rabbit, anesthesia was induced with intravenous ketamine hydrochloride (50 mg per kg of body weight; Ketamine, Yuhan, Korea) and 2% xylazine (0.1 mL/kg; Rompun, Bayer, Germany).

After anesthesia, bilateral back parallel to the spine was shaved and sterilized. Thereafter, 0.2 ml of VX2 tumor suspension was slowly implanted symmetrically in the bilateral paravertebral muscles at the level of the kidney each using 18-gauge Chiba needle under guidance of ultrasonography. Tumors were incubated for 10 - 12 days after the tumor implantation prior to baseline imaging. Among the 16 rabbits, the total number of tumors was 32. The longest diameter of the tumors on baseline T2-weighted axial MR images was 16.2 ± 3.5 mm (range, 9.3-22.2 mm).

Experimental Protocol

Sixteen rabbits were randomly allocated to receive injections of CKD-516 (Chong Kun Dang Pharmaceutical, Seoul, Korea) at a dose of 0.7mg/kg (n=11) or normal saline (n=6) (treated group and control group, respectively). One day after the baseline imaging, CKD-516 diluted in 3 mL of normal saline was administered slowly at a rate of 1 mL/min via the auricular vein to the treated group and the same

dose of normal saline to the control group. Follow-up imaging were performed 4 hours and 1-week after the administration. Among 16 rabbits, 4 rabbits in the treated group died during the experimental period.

PET/MRI image Acquisition

All acquisitions were performed by using an integrated PET/MRI scanner (Siemens Healthcare, Erlangen, Germany). All animals were fasted for at least 6 hours prior to the PET/MRI examination. Animals had an intravenous access established in the auricular vein at the day of PET/MRI acquisition. A dose of 37 MBq was intravenously injected and [^{18}F]-FDG PET/MRI was taken approximately 60 min after injection. MR acquisition was initiated as soon as the animals were placed in supine position in the scanner. Using three-plane, true-fast imaging with steady-state precession (true-FISP) localizers, an axial MRI slab was placed covering the whole tumor implant in paravertebral muscles. T2-weighted images (T2WI) were obtained with the following parameters: repetition time/echo time (TR/TE), 4230/84 ms; matrix size, 128x128; slice thickness, 3 mm; and field of view (FOV), 160x160 mm. Unenhanced T1-weighted volumetric interpolated breath-hold examination (VIBE) images were acquired at each flip angles for T1 mapping using the following parameters: TR/TE 3.2/1.1 ms; flip angles (α=2°, 5°, 10° and 15°); matrix size 128x128; slice thickness 3 mm; number of slices 20; and FOV 160 mm. Thereafter, dynamic contrast-enhanced MR imaging using the T1-weighted radial gradient echo sequence was then performed after an intravenous bolus injection via the auricular vein of 0.1mmol/kg of gadoteric acid (Dotarem; Guerbet, Paris, France). DCE-MRI using the VIBE sequence was obtained at 5

seconds of temporal resolution and the parameters were TR/TE 3.2/1.1 ms, flip angles (α=15°), matrix size 128x128, slice thickness 3 mm, number of slices 20, and FOV 160 mm. The total acquisition time of dynamic scan was 10 minutes, including the first 4 phases of pre-contrast images.

During MRI acquisition, emission data were collected from a single bed position of tumor implant level for 20 minutes list-mode dataset was acquired for all animals. Reconstruction of PET images was performed on the mMR console using 3D-ordered subset expectation maximization (3D-OSEM) with point spread function modeling with 3 iterations, 21 subsets, image matrix 256, a zoom factor of 2.

Image Analysis

The most commonly used two DCE-MRI parameters, the volume transfer coefficient (K^{trans}) and the initial area under the gadolinium concentration-time curve until 60 seconds (iAUC) were measured, according to the consensus opinion on DCE-MRI in evaluating vascular targeting agents in previous studies (1, 7, 15). Using the DCE-MRI images, parametric maps of K^{trans} and iAUC were generated with a post processing software program (Tissue4D; Siemens Medical Solutions) based on Tofts model (16, 17). We selected representative section with the longest diameter of tumor and drew a region of interest manually by outlining the entire tumor boundary.

The maximum and average standardized uptake value (SUVmax and SUVmean) were measured to determine FDG avidity of the tumors using commercial software (Syngo.via, Siemens Healthcare, Erlangen, Germany). A spheric-shaped volume of interest (VOI) that included

the entire lesion was drawn to determine FDG avidity. Metabolic tumor volume (MTV) was defined as total tumor volume with a 40% threshold of SUVmax value. Total lesion glycolysis (TLG) was calculated as (mean SUV) x (MTV).

Tumor size was defined as the longest diameter measured on axial T2-weighted images. In addition, tumor volume was measured using semi-automatic segmentation tool. Percentage changes in PET/MRI-derived parameters relative to baseline were calculated as follows: Value Change = $(Value_{giventime}-Value_{baseline})/Value_{baseline}*100\%$.

Statistical analysis

To determine whether there were differences in tumor size, volume PET/MRI imaging values and their interval changes between the treated and control groups, linear mixed model was used which made it possible to analyze clustered data, because each rabbit has two tumors. Spearman rank correlation test was performed to evaluate the correlation between the changes in PET/MR imaging values at each time point compared with baseline. A P value of less than .05 was considered to indicate a significant difference. All statistical analyses were performed with statistic package (SPSS, version21;SPSS, Chicago, IL, USA).

RESULTS

Among 16 rabbits, data from 3 rabbits (2 in treated group and 1 in control group) were incomplete because 1-week follow-up imaging were not available due to technical problems. In addition, 4 rabbits in treated group died unexpectedly before 1-week follow-up. Therefore 18 tumors in 9 rabbits (10 tumors in treated group and 8 tumors in control group) were available for all baseline, 4 hours and 1-week follow-up imaging.

Sequential change in size and volume of tumor

The size of tumors at baseline in the treated and control group was 15.20 ± 1.12 mm and 17.06 ± 1.45 mm, respectively and it showed no significant differences (P = 0.505). At 1-week follow-up, the tumors grew to 18.09 ± 1.24 mm and 22.56 ± 1.36 mm, respectively, and no significant differences were found between two groups (P = 0.133). Percentage change of size of tumors at 1-week follow-up were smaller in the treated group than in control group (19.70 % vs. 34.56 %, P = 0.037).

The volume of tumors at baseline in the treated and control group was 3.99 ± 1.64 cm^3 and 6.27 ± 2.51 cm^3, respectively and it showed no significant differences (P = 0.151). At 1-week follow-up, the tumors grew to and 8.14 ± 3.14 cm^3 and 13.34 ± 4.28 cm^3, respectively, and no significant differences were found (P = 0.056). Percentage change of volume of tumors at 1-week follow-up showed

no significant differences between the treated and control group (111.53 % vs. 120.38 %, P = 0.751).

Comparison of PET/MRI parameters at each time points and their changes between the treated and control group

The time * group interaction effect was found (P = 0.023) on linear mixed model analysis. Mean values of vascular and metabolic parameters and comparison of each parameter between treated and control group at each time points, as well as comparisons between different time points in each parameter are shown in Table 1 and Figure 1. Percentage changes of those relative to baseline for each group at each time point are summarized in Table 2.

There were no significant differences in all of PET/MRI parameters at baseline imaging between the two groups. At 4-hour follow-up, K^{trans} in treated group were lower than that in control group, although the difference showed no statistical significance (P = 0.055). iAUC in treated group were significantly lower than that in control group (P = 0.015) at 4-hour follow-up. At 1-week follow-up, MTV and TLG were significantly lower in treated group than those in control group (P = 0.035, respectively).

Percentage changes of PET/MRI parameters were also evaluated by using linear mixed model. Changes of K^{trans} and iAUC in the treated group were significantly larger compared with those in the control group at 4-hour follow-up (mean, -39.91 % vs. -6.04 %, P = 0.018; and -49.71% vs. +6.23%, P = 0.013). None of the relative change in

PET-derived parameters showed any statistical significant differences between the treated and control group at 4-hour follow-up.

MTV in the treated group significantly less increased compared with those in the control group at 1-week follow-up (mean, +118.34% vs. +208.87%, P = 0.003). No statistical differences were observed in percentage changes in SUVmax, SUVmean, TLG, K^{trans} and iAUC between the two groups at 1-week follow-up.

Comparison of PET/MRI parameters between the time points within each group

Serial measurements in treated group revealed that K^{trans} and iAUC decreased at 4-hour follow-up ($P < 0.001$, respectively) and partially recovered at 1-week follow-up (P = 0.001 and 0.024, respectively). MTV increased at 4-hour follow-up (P = 0.038) and further increased at 1-week follow-up ($P < 0.001$), while TLG increased at 1-week follow-up without significant difference ($P > 0.05$). In control group, K^{trans} and iAUC decreased at 1-week follow-up (P = 0.049 and 0.037, respectively). MTV increased at 4-hour follow-up (P = 0.018) and further increased at 1-week follow-up ($P < 0.001$), while TLG increased at 1-week follow-up (P = 0.001) in control group.

Correlation Analysis

To determine whether there is correlation between the percentage changes in parameters at 4-hour follow-up and change of tumor size or changes in parameters at 1-week follow-up for early prediction of tumor response, correlation analysis was performed in the treated group. Percentage change of TLG at 4-hour follow-up showed significant correlation with percentage change of MTV and TLG at

1-week follow-up with Spearman ρ of 0.673 and 0.782, respectively (P = 0.033 and 0.008, respectively).

DISCUSSION

Our study demonstrated that PET/MRI can show serial vascular and metabolic changes of intramuscular VX2 tumor model after administration of VDA, CKD-516. Vascular and metabolic parameters changed differently after the treatment with VDA. Significant differences in vascular parameters including K^{trans} and iAUC were observed after 4hours, whereas significant differences of metabolic parameters of MTV and TLG were observed at 1-week after VDA treatment between the control and treated group.

Our results of vascular parameters are similar to previous studies that have demonstrated that K^{trans} and iAUC values changed within a few hours after the treatment with VDA (7-9, 18). K^{trans} parameter reflect both blood flow and the endothelial permeability surface area, while iAUC reflect blood flow and endothelial permeability (3). Tumor blood vessels are immature and highly permeable, and lack of supporting connective tissues and VDA perturbs these preexisting vessels, leading collapse of tumor vasculature and subsequent necrosis (19). Thus, decrease of K^{trans} and iAUC reflects a decrease in blood flow and permeability in a tumor.

In addition to vascular parameters, we also demonstrated changes of metabolic parameters after the administration of CKD-516. Among PET-derived metabolic parameters, MTV and TLG showed significant differences at 1-week follow-up between the two groups, as well as percentage change of MTV at 1-week follow-up. MTV and TLG are potential biomarkers for predicting response to treatment as well as

for predicting prognosis in various solid tumors including head and neck cancer, lung cancer, esophageal cancer, cervical cancer, and epithelial ovarian cancer et al (20). Indeed, in the treated group, there were no significant differences in TLG at 1-week follow-up compared with baseline, while TLG values significantly increased at 1-week follow-up in the control group. Furthermore, change of TLG could be an early predictor for tumor response, as our results presented that the greater TLG changed at 4 hours follow-up, the greater MTV and TLG changed at 1-week follow-up.

To our knowledge, this is the first study that depicts multiparametric monitoring of tumor response after the administration of VDA, using the novel imaging technique, PET/MRI. Multimodality imaging is a fast-growing field in clinical practice, but most are performed on separate machines, which requires time-consuming processing and manipulating the vast amount of imaging. Also, side-by-side interpretation of images results in diagnostic inaccuracy (21). If we assess tumor response after the VDA treatment with multiparametric imaging with each modality, DCE-MRI should be performed 4 hours, while PET should be performed 1-week later after the treatment as our results showed. Thus, integration and interpretation of different modality at different times would be logistically demanding. However, PET/MRI has advantage in capability of obtaining multiparametric information simultaneously, thus we can evaluate both vascular and metabolic parameters at different time points with one imaging modality.

Our study has several limitations. First, we conducted baseline imaging 1 day before the administration of CKD-516 considering

elimination of previous injected [^{18}F]-FDG. Because VX2 tumor is highly aggressive and grows rapidly (22), microenvironment of the tumor would change within a day. Thus, changes of parameters at 4 hours after the treatment may include not only the effect of drug but also intrinsic change of tumor characteristics. Second, DCE-MRI parameters are measured with one axial cross sectional image, which might be less representative of the entire tumor. Third, it is not validated whether early changes in vascular and metabolic parameters in PET/MRI after the treatment with VDA is relevant with clinical outcome such as overall survival, so further studies must be performed.

In conclusion, PET/MRI is able to monitor the change of vascular and metabolic parameters at different time points simultaneously, and confirmed that vascular changes precede the metabolic changes by VDA, CKD-516.

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TABLES AND FIGURES

Table 1. Comparison of vascular and metabolic parameters between the control and treated groups at each time point and *P* values of comparisons between different time points in each parameter

Control (n=8)				Treated (n=10)				
		P Value				*P* Value		*P* Value
Ktrans (min-1)		4 Hours	1 Week	Ktrans (min-1)		4 Hours	1 Week	
Baseline	0.29 ± 0.13	NS	0.049	Baseline	0.28 ± 0.69	<.001	0.001	0.816
4 Hours	0.26 ± 0.08		NS	4 Hours	0.16 ± 0.05		NS	0.055
1 Week	0.19 ± 0.06			1 Week	0.20 ± 0.07			0.903
iAUC (mmol/sec)				iAUC (mmol/sec)				
Baseline	27.85 ± 10.39	NS	0.037	Baseline	26.49 ± 5.82	<.001	0.024	0.819
4 Hours	28.31 ± 8.30		0.014	4 Hours	12.95 ± 5.44		<0.001	0.015
1 Week	18.58 ± 5.22			1 Week	21.23 ± 7.76			0.555
SUVmax				SUVmax				
Baseline	8.72 ± 2.91	NS	NS	Baseline	6.44 ± 2.00	NS	NS	0.221
4 Hours	6.91 ± 3.01		NS	4 Hours	5.77 ± 1.80		NS	0.524
1 Week	8.79 ± 2.70			1 Week	5.52 ± 2.59			0.105

SUVmean				SUVmean				
Baseline	5.50 ± 2.02	NS	NS	Baseline	4.00± 1.22	NS	NS	0.228
4 Hours	4.37 ± 1.91		NS	4 Hours	3.50 ± 1.14		NS	0.446
1 Week	5.21 ± 1.59			1 Week	3.19 ± 1.56			0.099
MTV(cm^3)				MTV(cm^3)				
Baseline	3.78 ± 2.01	0.018	<.001	Baseline	2.81 ± 1.09	0.038	<.001	0.374
4 Hours	4.65 ± 2.00		<.001	4 Hours	3.66 ± 0.91		0.005	0.345
1 Week	10.69± 4.02			1 Week	6.09 ± 2.17			0.035
TLG(cm^3)				TLG(cm^3)				
Baseline	23.96 ± 21.28	NS	0.001	Baseline	10.66 ±3.64	NS	NS	0.225
4 Hours	21.67 ± 13.47		0.001	4 Hours	12.41 ± 4.33		NS	0.193
1 Week	60.23 ± 35.20			1 Week	18.93 ± 12.85			0.035

Data are presented as mean ± standard deviation.

K^{trans}:volumetransfercoefficient

iAUC: initial area under the gadolinium concentration-time curve until 60 seconds

SUV: standardized uptake value

MTV: metabolic tumor volume

TLG: total lesion glycolysis

Table 2. Percentage changes of vascular and metabolic parameters compared with the baseline at each time point and *P* values of comparisons between the control and treated group.

	Control (n=8)	Treated (n=10)	*P* Value
$K^{trans}(min^{-1})$			
4 Hours	-6.04(-21.04, 8.97)	-39.91(-52.64, -27.18)	0.018
1 Week	-29.90(-66.07, 6.27)	-27.35(-45.62, -9.08)	0.822
iAUC (mmol/sec)			
4 Hours	6.23(-17.75,30.21)	-49.71(-65.47, -33.95)	0.013
1 Week	-24.15(-53.84,5.55)	-18.87(-38.17, 0.43)	0.797
SUVmax			
4 Hours	-15.57(-52.41, 21.27)	-7.97(-25.83, 9.89)	0.757
1 Week	4.89(-23.17, 32.95)	-16.42(-35.03, 2.18)	0.299
SUVmean			
4 Hours	-14.82(-51.87, 22.23)	-10.05(-30.41, 10.30)	0.852
1 Week	-0.76 (-27.03, 25.51)	-21.92(-42.63, -1.21)	0.303

MTV (mL)			
4 Hours	30.74(14.05, 47.72)	37.82(16.61, 59.03)	0.660
1 Week	208.87(145.75, 272.00)	118.34(76.59, 160.10)	0.044
TLG (cm^3)			
4 Hours	195.96(129.96, 261.97)	42.23(2.68, 81.77)	0.623
1 Week	209.64(108.00, 311.28)	79.43(3.74, 155.14)	0.101

Data are relative percentage changes determined by comparing the value at baseline with that at follow-up. Data in parentheses are 95% confidence intervals.

K^{trans}:volumetransfercoefficient

iAUC: initial area under the gadolinium concentration-time curve until 60 seconds

SUV: standardized uptake value

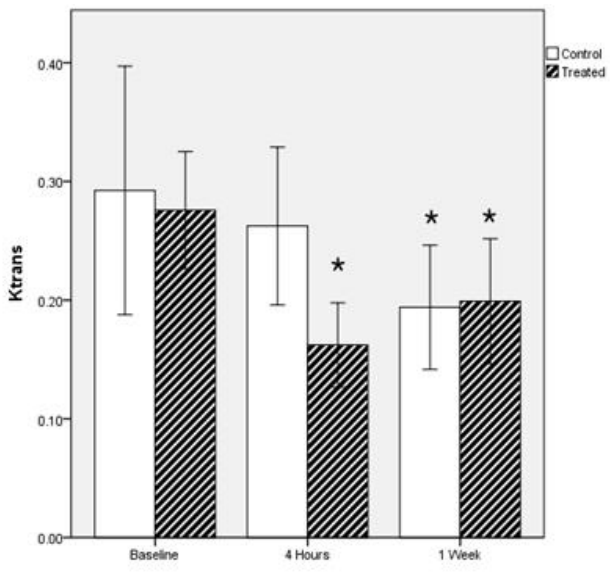
MTV: metabolic tumor volume

TLG: total lesion glycolysis

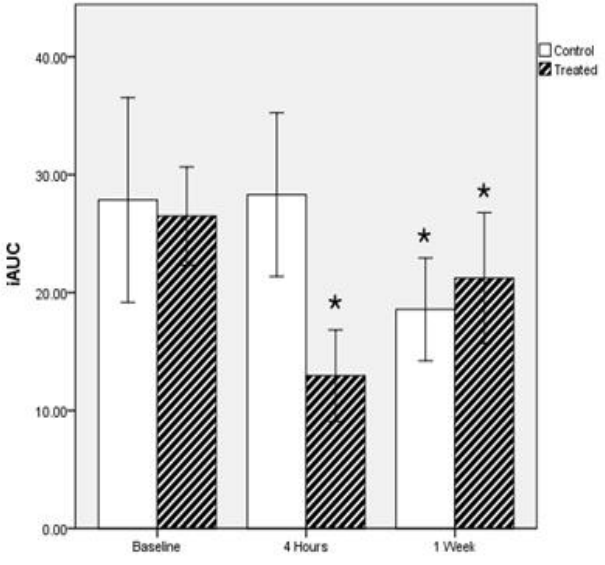
Figure 1. Serial measurement of (a) Ktrans, (b) iAUC, (c) SUVmax, (d) SUVmean, (e) MTV and (f) TLG at different time points. * is significant change compared to the baseline.

K^{trans}:volumetransfercoefficient
iAUC: initial area under the gadolinium concentration-time curve until 60 seconds
SUV: standardized uptake value
MTV: metabolic tumor volume
TLG: total lesion glycolysis

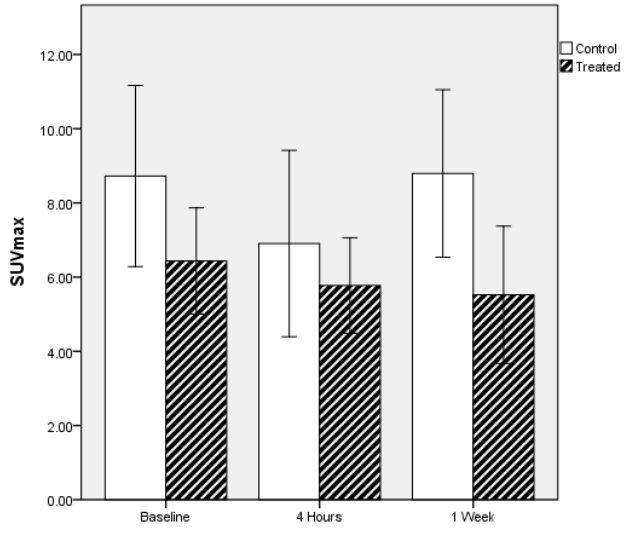
(a)


Control
Treated
Ktrans
0.40
0.30
0.20
0.10
0.00
Baseline
4 Hours
1 Week
*
*
*
*

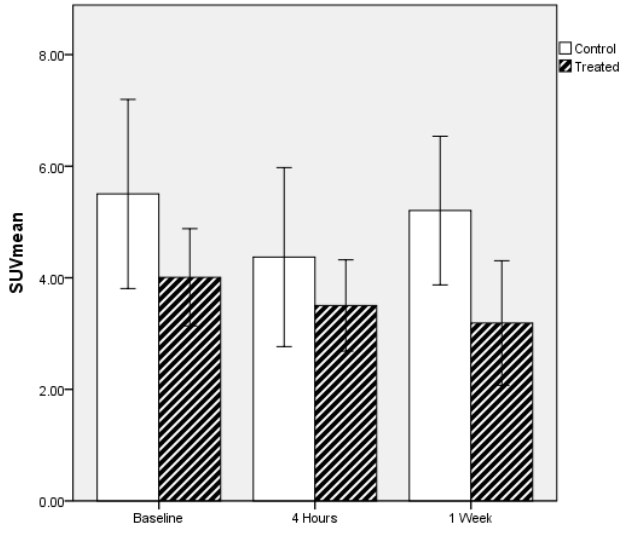
(b)


Control
Treated
iAUC
40.00
30.00
20.00
10.00
0.00
Baseline
4 Hours
1 Week
*
*
*
*

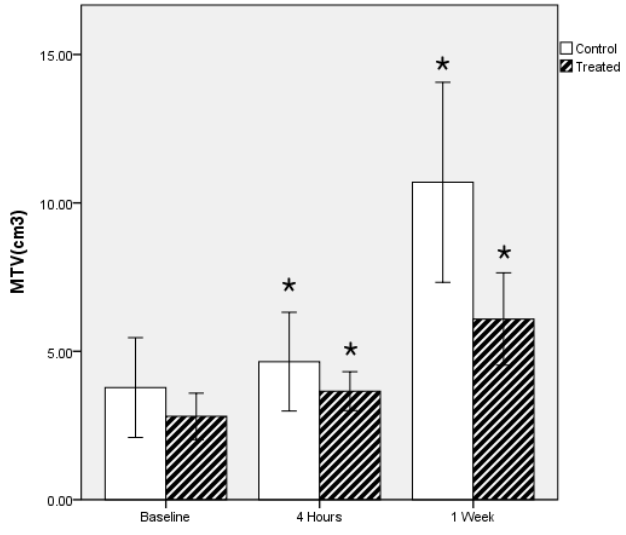
(c)


SUVmax
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Baseline
4 Hours
1 Week
Control
Treated

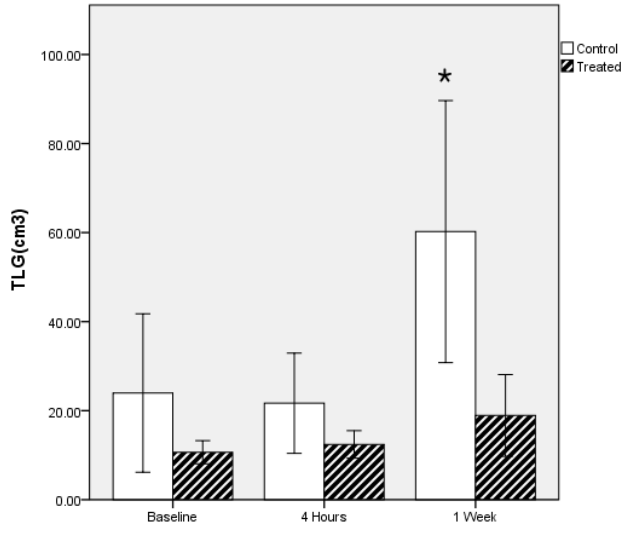
(d)


SUVmean
8.00
6.00
4.00
2.00
0.00
Baseline
4 Hours
1 Week
Control
Treated

(e)


MTV(cm3)
15.00
10.00
5.00
0.00
Baseline
4 Hours
1 Week
Control
Treated
*
*
*
*

(f)


TLG(cm3)
100.00
80.00
60.00
40.00
20.00
0.00
Baseline
4 Hours
1 Week
Control
Treated
*

요약 (국문초록)

토끼종양모델에서 양전자단층촬영-자기공명영상(PET/MRI)을 이용한 혈관차단제 CKD-516에 대한 반응 평가: 혈류 및 대사 파라미터의 동시 평가

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목적 : 토끼종양모델을 이용하여 CKD-516 투여 후 나타나는 혈류 및 대사 관련 파라미터의 변화를 PET/MRI을 이용하여 확인하고자 하였다.

방법 : 양측 척추 옆 근육에 이식한 18개 VX2 종양을 지닌 9마리의 토끼에서 실험군에서는 CKD-516을, 대조군에서는 생리식염수를 주입 전, 주입 후 4시간, 1주일 후 양전자단층촬영-자기공명영상(PET/MRI)을 촬영하여 체적전이상수 (volume transfer coefficient, K^{trans}),60초 농도곡선 하 초기 면적 (initial area under the gadolinium concentration-time curve until 60 seconds, iAUC), 최대 표준 섭취 계수 (maximum standardized uptake value, SUVmax), 평균 표준 섭취 계수(average standardized uptake value, SUVmean), metabolic tumor volume (MTV), total lesion glycolysis (TLG)를 분석하였다. 치료군 및 대조군에서 파라미터 값 및 그 변화량의 차이는 linear mixed model을 이용하

여 검정하였다. 각 군에서 파라미터 값의 연속적인 변화 또한 linear mixed model을 이용하여 검정하였다.

결과 : 주입 전과 비교하였을 때 4시간 후 K^{trans}및 iAUC의 값의 감소가 치교군에서 대조군에 비해 유의하게 컸다 (mean, -39.91% vs. -6.04%, P = 0.018; -49.71% vs. +6.23%, P = 0.013). 또한 1 주일 후, MTV의 증가량이 유의하게 작았다 (mean, +118.34% vs. +208.87%, P= .044). 치료군에서 K^{trans}및 iAUC는 4시간 후에 유의하게 감소하였고 (P < 0.001), 1주일 후 부분적으로 회복되었다 (P = 0.001 and 0.024, respectively). MTV는 4시간 후에 증가하였고 (P = 0.038) 1주일 후 더 증가하였다 (P < 0.001).

결론 : PET/MRI는 CKD-516 투여 후 서로 다른 시기에 나타나는 혈류 및 대사 관련 파라미터의 변화를 평가할 수 있으며 혈류의 변화가 대사의 변화에 선행하는 것을 확인하였다.

주요어: PET/MRI, 혈관 차단제, 치료 반응, 혈류 파라미터, 대사 파라미터

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