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ORIGINAL ARTICLE
ORJİNAL ARAŞTIRMA

Time-Resolved Contrast-Enhanced Magnetic Resonance Angiography Versus Digital Subtraction Angiography in Internal Carotid Artery Stenosis

İnternal Karotid Arter Darlıklarında Time-Resolved Kontrastlı Manyetik Rezonans Anjiyografi ve Dijital Substraksiyon Anjiyografinin Karşılaştırılması

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ÖZ

Amaç: Bu çalışmada, inme ve serebrovasküler hastalık semptomları olan hastalarda internal karotid arter darlığını saptamada, dijital substraksiyon anjiyografi (DSA) referans alınarak TRICKS MRA tekniğinin duyarlılık, özgüllük, olumlu ve olumsuz öngörü değerleri ve tanısal doğruluğu araştırılmıştır.

Materyal ve Metodlar: Bu çalışmaya, Nisan 2009-Kasım 2010 tarihleri arasında, toplam 22 (16 erkek, 6 kadın) olgu dahil edilmiştir. MRA incelemeleri, 1.5 Tesla MR görüntüleme sisteminde yapılmıştır. Her olgunun MRA ve DSA görüntüleri, birbirinden bağımsız iki radyolog tarafından değerlendirilmiştir. İCA stenoz oranı NASCET yöntemine göre sagittal plandaki MR anjiyografik maksimum yoğunluk projeksiyonları ve lateral plandaki DSA görüntüleri üzerinden saptanmıştır.

Bulgular: Tüm segmentleri boyunca 44 İCA, TRICKS MRA ve DSA ile 56 stenoz noktasında karşılaştırıldı. Gözlemciler arası uyum k istatistiğine göre her iki yöntem için de çok iyi ve mükemmel düzeyde olup TRICKS MRA için 0.73 ve DSA için 0.83'dür. TRICKS MRA'nın %70-99 aralığında stenozu öngörmede birinci ve ikinci gözlemciye göre duyarlılığı; %100 ve %100, özgüllüğü %92,3 ve %94,2, PPV %50 ve %50, NPV %100 ve %100 olarak saptanmıştır.

Sonuç: ICA stenozlarının saptanmasında yüksek tanısal doğruluk oranlarıyla TRICKS MRA'nın, komplikasyon riski yüksek, invaziv bir yöntem olan DSA'ya alternatif olarak kullanılabileceği düşünülmektedir.

Anahtar kelimeler: Dijital subtraksiyon anjiografi, İnternal karotid arter stenozu, Zaman-çözünürlü kontrastlı manyetik rezonans anjiografi

ABSTRACT

Objectives: In this study, digital subtraction angiography (DSA) being taken as a reference, the sensitivity, specificity, positive and negative predictive values (PPV and NPV), and diagnostic accuracy of time-resolved imaging of contrast kinetics magnetic resonance angiography (TRICKS MRA) was used in the detection of ICA stenosis in patients with stroke and cerebrovascular disease symptoms.

Materials and methods: From April 2009 to November 2010, 22 (16 male, 6 female) consecutive patients were included in this study. MRA was performed 1.5 Tesla MR. Results of TRICKS MRA, and DSA were read independently by two observers. ICA stenosis was measured according to the following North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. From the MR angiographic maximum intensity projections (MIP), the percentage of ICA stenosis was assessed on sagittal projection, which coincided with the lateral of the DSA projections used.

Results: All segments throughout in 44 ICA's compared at 56 point of stenosis in TRICKS MRA and DSA. The k statistics that reflected the interobserver variability between observers 1 and 2 were very good and similar for two tests: 0.73 for TRICKS MRA, and 0.83 for DSA. In the 70-99% carotid artery stenosis range, according to first and second independent observation, TRICKS MRA has a sensitivity of 100% and 100%; specificity of 92.3% and 94.2%; PPV of 50% and 50%, NPV of 100% and 100%, respectively, compared to digital subtraction angiography.

Conclusion: TRICKS MRA which has high rates of diagnostic accuracy on determining ICA stenoses could be considered as an alternative for invasive DSA which has higher risk of complications.

Key words: Digital subtraction angiography, Internal carotid artery stenosis, Time-resolved contrast-enhanced magnetic resonance angiography

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Introduction

Eighty percent of the strokes are caused by ischemia, of those, 20% is caused by stenosis of the carotid artery (1). Atherosclerosis is the underlying factor in 90% of thromboembolic events. The most important source of emboli is carotid artery stenosis (2). Atherosclerotic lesions are specifically located in the proximal 2 cm of ICA. The risk of stroke is increased by the rate of stenosis and morphology of the plaque. 70% stenosis is considered by experts to be the threshold value (3). Many studies performed on symptomatic and asymptomatic patient groups showed that carotid endarterectomy resulted in reduced rates of transient ischemic attack, stroke and death in the long term (4). This emphasizes the importance of characterizing the degree of stenosis accurately.

Three-dimensional (3D) time-resolved MRA, is one of the best application of parallel imaging methods in the field of MRA. Serial images are taken using a rapid imaging modality in a specific time period during the injection of contrast, as in DSA. 3D MIP images are then obtained from those images. By this method, venous contamination in areas with high cerebral venous return is negated. This method is quite effective in evaluating the flow and the filling mechanics of vascular lesions. 3D time-resolved contrast-enhanced MRA provides both anatomical and hemodynamic data (5). In addition, pure arterial or pure venous phase images can be rapidly obtained. This technique is currently used for extra-cranial carotid artery imaging.

In this study, the differences between diagnostic 3D TRICKS MRA and diagnostic and therapeutic DSA in patients with a pre-diagnosis of carotid artery stenosis and cerebrovascular disease were evaluated retrospectively. Diagnostic reliability of 3D TRICKS MRA in the diagnosis of carotid artery stenosis was investigated via sensitivity, specificity, PPV, and NPV results. These paramaters were compared with DSA which is the gold standard in the diagnosis of the carotid artery stenosis.

Materials and methods

Twenty-two patients with pre-diagnosed carotid artery stenosis and cerebrovascular disease between April 2009 to November 2010 were included in the study. Sixteen patients were male and 6 were female. They underwent both time-resolved contrast MRA and DSA examinations in short time intervals (between one day and one month). The study protocol was approved by the local institutional ethics committee (number: B.30.2.GOÜ.0.01.00.00/7U).

All MR angiographies completed in the study were performed using a 1.5 T imaging system (Signa excite HDx12.0 M5B software; GE Healthcare, Milwaukee, WI, USA, 2005). Neurovascular head and neck coils (General Electric, 1.5T, 8 Ch) were also used. After the injection of the contrast, images were obtained, in the coronal plane extending from the aortic arch to the circle of Willis ring by using the 3D TRICKS sequence (TR: 4.1, TE: 1.6, NEX: 0.75, Angle of drift (FA): 35°, effective slice thickness 1 mm (slice thickness: 1.8 mm, ZIP 2), FOV: 28x20 cm, matrix: 320x224, band width: 62.5, voxel volume: 1.1x1.3x1.0 mm). Slap thickness were set to include carotid and vertebral arteries. The number of cross sections were 60-70 images in one series; imaging time was between 1.10 to 1.30 seconds. Processing time was approximately 5 minutes. Elliptical-centric method was used for calculating the K-area.

Contrast agent with a dose of 0.1 mmol/kg was injected with an automatic injector using a 22 G canula in the antecubital vein at a speed of 1.5 ml/s. After the injection of contrast, the catheter was flushed with 20 ml of isotonic NaCl. The contrast agent used was gadobenat dimeglumin (MultihanceR-0.5 mol/L; Bracco, Milan, Italy). 20 seconds after the initiation of the sequence, 0.1 mmol/kg of contrast agent was given in 26.6 seconds by the automatic injector. Volume images were reconstructed every 5 seconds in order to demonstrate the temporal resolution in every frame. Subtracted images were formed by using the first volume as a mask.

Three dimensional images were constructed by using the basal images in the"GE Advantage Windows Workstation 4.2", "Volume Viewer" program via the MIP algorithm. Three dimensional images were formed including the internal carotid artery bifurcation and the more distal segments without missing any level; most stenotic segments were found and analysed in the adequate magnification on sagittal projections.

DSA examination was performed using the DSA GE Innova 3100 (Milwaukee-USA) angiography device. Images were obtained by 1000x1000 and 750x750 matrices. In all of the cases included in the study, carotid artery imagings were obtained by using 10 ml of iodine contrast (Omnipaque, 350 mg of iodine per milliliter; GE) given at a speed of 5 ml/s for each carotid artery following femoral artery catheterization with the Seldinger method in the posteroanterior and lateral projections by 4F and Simmons catheters via selective catheterization. Stenosis measurements were calculated by "GE Advantage Windows Workstation 4.3", in the most stenotic segments in the lateral projections.

In the carotid system, the level of the bifurcation and all the segments of the internal carotid artery were evaluated. MRA and DSA images of all cases were analysed by two experienced radiologists in neurovascular radiology. Rates of stenosis were determined. Each of the observers independently evaluated the MRA images first, and then the DSA images at different times without knowing the evaluation of the other observer. The other images were hidden from the observers during the evaluation of an image. In each method, measurement of the most stenotic part was taken and the rate of stenosis was determined by the NASCET method. DSA images in the lateral projection and MIP images in the sagittal plane of MRA were used during the measurements (fig 1). DSA was accepted as gold standard method. Stenosis rates in the carotid bifurcation level and internal carotid artery were divided into 5 groups: < 30%, 30-49%, 50-69%, 70-99%, 100% (obstructed).

The presence of significant difference between DSA and TRICKS MRA in the evaluation of stenosis was determined by Marginal Homogeneity and McNemar tests (In the dependent groups with Ki-Square tests). Diagnostic consistency between DSA and TRICKS MRA was evaluated by Kappa Coefficient(κ) . Sensitivity, specificity, PPV, NPV and diagnostic accuracy rate were calculated in order to evaluate the diagnostic efficacy of MRA compared to DSA. Diagnostic accuracy rate was calculated as the rate of the referrence method (TRICKS MRA) to correctly classify the cases in comparison with the gold standard (DSA). Continuous variables were shown by average (Avg) and standard deviation (SD); categorical variables were shown by number (n) and percentage (%). P values were accepted as statistically significant when they were below 0.05. Calculations were performed using statistical software (PASW ver.18, SPSS inc. Chicago, IL).

Results

Fifty-six segments from 44 internal carotid arteries of 22 patients were included in the study. The age range of these patients was 45 to 84 years (average 68±10 SD). The distribution of the stenotic segments according to the observers based on the NASCET classification are presented in Tables 1 and 2. The consistency between the observers in DSA and 3D TRICKS MRA techniques were statistically significant(P<0.001). Kappa coefficient was 73.3% in 3D TRICKS MRA, the consistency was high; kappa coefficient for DSA was 83.6% and the consistency was perfect.

Table 1: The distribution of the stenotic segments according to the first observer in DSA and TRICKS MRA images, based on the NASCET classification

Observer 1		DSA 0-29% (n=29)	DSA 30-49% (n=11)	DSA 50-69% (n=9)	DSA 70-99% (n=4)	DSA 100% (n=3)	DSA Total (n=56)
TRICKS MRA	0-29%	24 (82,7%)	3 (27,2%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	27 (48,2%)
	30-49%	4 (13,7%)	4 (36,3%)	1 (11,1%)	0 (0,0%)	0 (0,0%)	9 (16,0%)
	50-69%	1 (3,4%)	3 (27,2%)	5 (55,5%)	0 (0,0%)	0 (0,0%)	9 (16,0%)
	70-99%	0 (0,0%)	1 (9,1%)	3 (33,3%)	4 (100%)	0 (0,0%)	8 (14,2%)
	100%	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	3 (100,0%)	3 (5,3%)

At the 70-99% internal carotid artery stenosis interval, MRA had a sensitivity of 100%, specificity of 92.3%, PPV of 50%, NPV of 100% and diagnostic accuracy of 92.8% when compared with DSA according to the first observer. According to the second observer, in the same carotid artery stenosis interval MRA had sensitivity of 100%, specificity of 94.1%, PPV of 50%, NPV of 100% and diagnostic accuracy of 94.6% when compared with DSA. Kappa coefficient in the 70-99% stenosis level was 63.2% for the first observer, 74.1% for the second observer and the level of consistency was very good.

Table 2: The distribution of the stenotic segments according to the second observer in DSA and TRICKS MRA images, based on the NASCET classification

Observer 2		DSA 0-29% (n=30)	DSA 30-49% (n=10)	DSA 50-69% (n=8)	DSA 70-99% (n=5)	DSA 100% (n=3)	DSA Total (n=56)
TRICKS MRA	0-29%	28 (93,3%)	3 (30,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	31 (55,3%)
	30-49%	0 (0,0%)	4 (40,0%)	2 (25,0%)	0 (0,0%)	0 (0,0%)	6 (10,7%)
	50-69%	2 (6,6%)	2 (20,0%)	4 (50,0%)	0 (0,0%)	0 (0,0%)	8 (14,2%)
	70-99%	0 (0,0%)	1 (10,0%)	2 (25,0%)	5 (100%)	0 (0,0%)	8 (14,2%)
	100%	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	3 (100,0%)	3 (5,3%)

Diagnostic accuracy and consistency values according to the classified ranges are shown in Table 3.

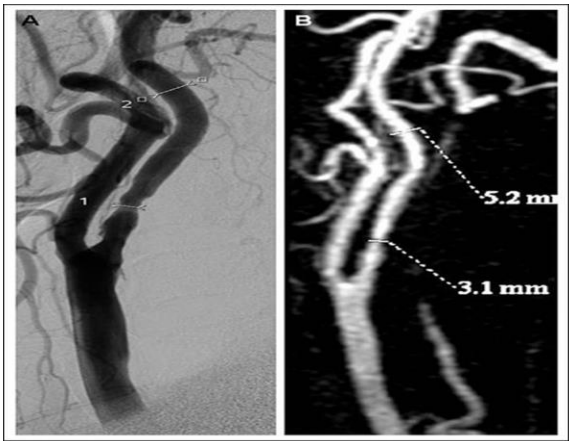

Figure 1. Measurement of ICA stenosis according to NASCET methods. 76 year old male patient. DSA image in lateral projection (A) 3D TRICKS MRA MIP image in sagittal projection (B) (According to the first observer there was 49% stenosis in DSA, 41% stenosis in TRICKS MRA.).

According to the first observer, of the 8 segments of vessels in the 70% to 99% stenosis range in TRICKS MRA, four were concordant with DSA. For the second observer, of the 8 segments of vessels in the 70% and 99% stenosis range in TRICKS MRA, five were concordant with DSA (fig 2).

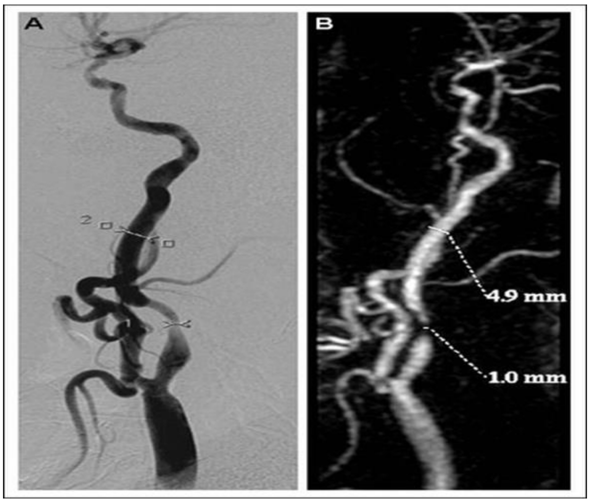

Figure 2. 73 year old male patient. DSA image in lateral projection (A) 3D TRICKS MRA MIP image in sagittal projection (B) (According to the second observer, there was 73% stenosis in DSA, 80% stenosis in TRICKS MRA.).

The four vessel segments which were discordant with the DSA acccording to the first viewer and the three vessel segments discordant with DSA acccording to the 2nd viewer were all located in the lower stenosis ranges. Acccording to the first observer, three were considered to be in the 50-69% stenosis range, and one in the 30-49% stenosis range.

For the second observer, two were considered to be in the 50-69% stenosis range, and two in the 30-49% stenosis range. The sensitivity of MRA in stenosis of greater than 70% was 100% for both observers; specificity was 92.3% for the first observer, and 94.1% for the second observer.

Tablo 3: Diagnostic efficacy of TRICKS MRA in comparison with DSA at different stenotic ranges of the internal carotid artery.

	Observer 1					**Observer 2**				
NASCET Classification	**0-29%**	**30-49%**	**50-69%**	**70-99%**	**100%**	**0-29%**	**30-49%**	**50-69%**	**70-99%**	**100%**
Sensitivity	82.7%	36.3%	55.5%	100%	100%	93.3%	40.0%	50%	100%	100%
Specificity	88.8%	88.8%	92.1%	92.3%	100%	88.4%	95.6%	91.6%	94.1%	100%
PPV	88.8%	44.4%	55.5%	50%	100%	90.3%	66.6%	50%	50%	100%
NPV	82.7%	85.1%	92.1%	100%	100%	92.0%	88.0%	91.6%	100%	100%
Diagnostic Accuracy	85.7%	78.5%	91.0%	92.8%	100%	91.0%	85.7%	85.7%	94.6%	100%
κ	0,679	0,271	0,470	0,632	1,000	0,747	0,423	0,417	0,741	1,000

For detecting the stenosis levels above 70%, DSA and MRA had a very high concordance.(For the first observer κ=0.632; for the second observer κ=0.741 and P<0.001. The concordance of carotid artery stenosis rates between DSA and TRICKS MRA according to the observers are shown in Figures 3 and 4.

Discussion

Non invasive methods are widely used in the first step of the evaluation of carotid artery stenosis. Currently, the most reliable method is DSA prior to surgery or endovascular treatment. DSA is accepted as the gold standard method in the diagnosis of obstructive supraaortic vascular lesions. It has well defined morbidity rate (0.5-4%) and mortality rate (0.01%). Morbidities include ionizing radiation, nephrotoxicity of the contrast material, and long recovery period. It is also expensive (6-8). Thus non-invasive methods are preferred more often. Methods like Doppler ultrasonography, computed tomography angiography and MRA have high sensitivity and specificity in the diagnosis of the carotid stenosis ranging from 70% to 99% (9).

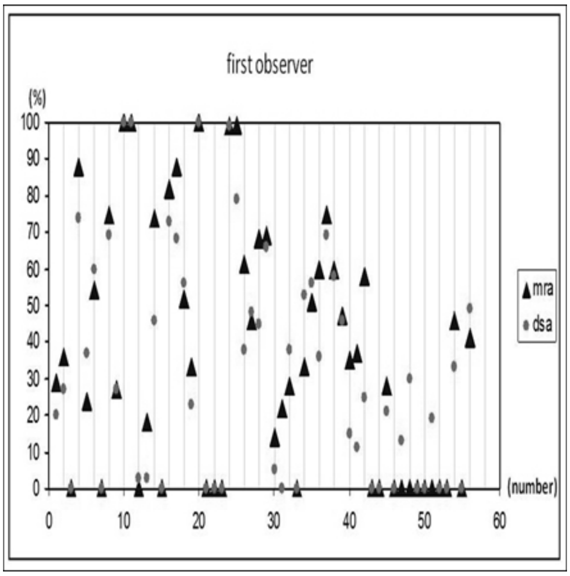

Figure 3. Concordance of carotid artery stenosis rates between DSA and TRICKS MRA according to the first observer.

Contrary to the known complications of DSA, MR imaging and MRA have very low complication rates. Special attention must be paid in patients with decreased renal function to avoid the risk of nephrogenic systemic fibrosis (10).

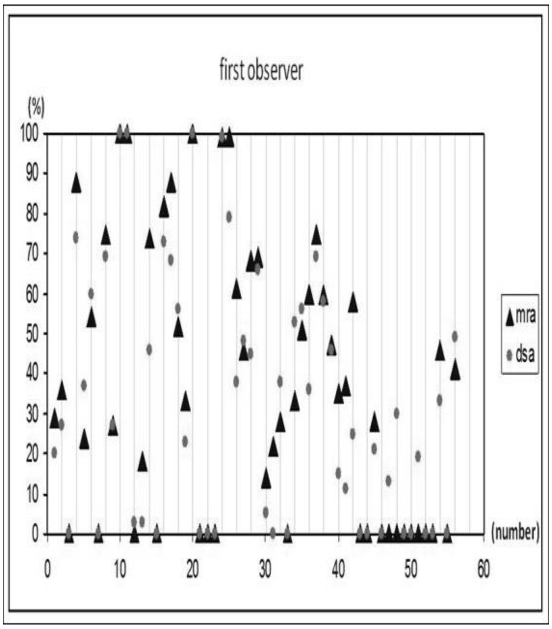

Figure 4. Concordance of carotid artery stenosis rates between DSA and TRICKS MRA according to the second observer.

An advantage of MRA over DSA in the imaging of the carotid bifurcation is the ability to obtain several images with a single contrast agent administration in MRA; in contrary, DSA requires at least two injections for the standard biplan images. The most significant advantages of contrast MRA are less artifact caused by flow and patient movement, and obtaining good spacial resolution of a wide area from the aortic arch to circle of Willis. This allows us to estimate the level of stenosis of the internal carotid artery more accurately and make differential diagnoses between occlusion or pseudo occlusion, which is clinically and therapeutically very important. It also allows us to visualize strings of stenotic areas (11).

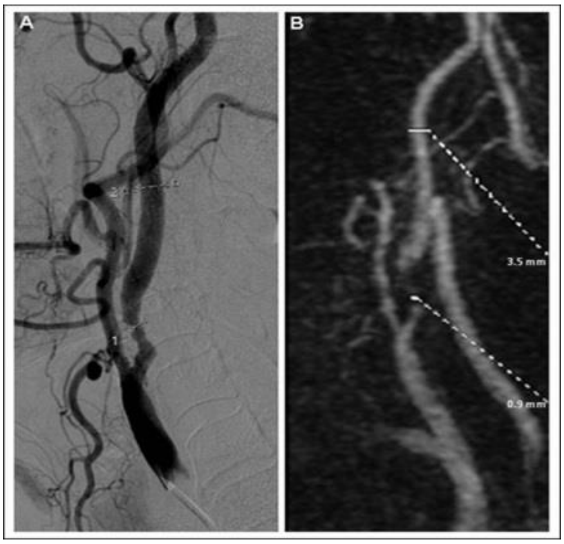

Figure 5. 72 year old female patient. DSA image in lateral projection (A) 3D TRICKS MRA MIP image in sagittal projection (B) (According to the first observer there was 69% stenosis in DSA, 75% stenosis in TRICKS MRA.)

Anzalone et al. in their series of 49 patients with carotid artery stenosis where 3D TOF MRA, contrast MRA, DSA and rotational angiography were compared, found that the best concordance were between contrast MRA and rotational angiography and versus DSA and rotational angiography. In the study, the area of stenosis was evaluated on multiple projections by MRA. MRA provided the opportunity to measure the most stenotic lumen; but when compared with DSA, MRA led to over-measurement of the stenosis (12).

In a study performed by Yang et al. which compared contrast MRA with DSA, in stenosis or occlusions more than 50% MRA had 92-100% sensitivity and 97-99% specificity; in cases with 100% occlusion it had 92-100% specificity and 97-99% specificity 97-99% (13). In the study performed by Nederkoorn et al. with 51 cases in the 70-99% stenosis range, contrast MRA had 90-91% sensitivity and 76-77% specificity (14). The reason for this statistically significant difference between these studies is likely attributed to the more inclusive selection of 50-99% stenosis range in the study done by Yang et al., compared to 70-99% stenosis range in the study done by Nederkoorn et al. (13,14).

In a study performed by Randoux et al. with 22 cases, sensitivity was 93% and specificity was 100%. They concluded that MRA was a reliable diagnostic method which could replace DSA (15).

DeMarco et al. showed that when high resolution contrast-enhanced MRA was combined with contrast timing of bolus and automatic triggering, it was more efficient. In this study, elliptical central phase application was used. In 63 patients, bolus access time was reported as 17.4 seconds on average. 95% success was achieved and 98% of the applications were perfect. Two independent observers report that the contrast images were statistically significant (P<0.001). Ulceration, slow flow and the length of the stenosis were detected better in the MR images. While artifacts from slow flow saturation and carotid artery stenosis were seen in multi-slab 3D images, they were not seen with the contrast application. Authors report the equality or the superiority of contrast MRA in detection of carotid stenosis over multislab 3D TOF (16).

TRICKS MRA has many advantages when compared to MRA techniques with and without contrast. This technique was named as TRICKS as k-space sampling techniques were combined to shorten the imaging time. Contrast optimizes the data kinetics while the bolus runs through the vessel (5). In the TRICKS technique, data obtained while the temporal resolution is imaged every 2-6 seconds allows data to be render in three dimensions. Thus, series can be formed equivalent to conventional angiography (17). Data acquisition starts before the injection of the contrast, so that precontrast series are obtained to enhance the vessel visibility. Background signals are effectively eliminated and the technique allows for multiple injections of contrast during the same application. Several k-space sampling raters are used in the technique and k-space elements in between the image sets are shared. With this technique the passage of the contrast can be followed first in the artery than in the vein. It is minimally sensitive to contrast timing allowing retrospective post processing volume images. Coordination of the access time for the bolus is less critical, as the images start to be obtained before the injection and continue in the arterial and venous phases. Identifying seriously diseased vessels is important. Thus TRICKS can show vessels which opacifiy very late in the angiographic series (18,19).

Remonda L. et al. in their study of 120 patients comparing the time resolved MRA with contrast and the DSA, the concordance of MRA with contrast and DSA was 93% in the 70-99% stenosis range. The sensitivity and specificity in all stenosis ranges in MIP images was 98% and 96%, respectively. In the 0-29% stenosis range, the concordance between MRA and DSA was 90%. In the 30-69% stenosis range the concordance was 68% (11).

In our study, we compared a MRA technique with contrast called 3D TRICKS MRA with DSA according to the stenosis rate calculated by the NASCET method. Base on our results, the sensitivity and specificity of

MRA in diagnosis of the stenosis in the 70-99% range was 100% and 92.3% for the first observer; 100% and 94.1% for the second observer. In the 70-99% stenosis range, 3D TRICKS MRA had high sensitivity and specificity consistent with values in the literature.

In our study, 16 of 56 vessel segments under MRA according to the first observer and 12 segments according to the second observer were qualified at different stenosis ranges. When compared according to the first observer, of the 16 vessel segments which were classified in different stenosis ranges in MRA, 12 were classified in higher stenosis levels than DSA, 4 were classified in lower stenosis levels than DSA. According to the second observer, of the 12 vessel segments which were classified in different stenosis ranges in MRA, four were classified in lower stenosis levels than DSA. When the vessels classified as being in the lower stenosis levels in MRA compared to DSA were reexamined, it was thought that spatial resolution of the MRA was lower than DSA and the signal noise ratio was possibly low.

U-King-Im JM et al. compared MRA with contrast and DSA; one of the limitations was critical stenosis levels had a sharp cut-off point of 70% according to NASCET and European Carotid Surgery Trial methods. Stenosis levels like 67%, which as minimal clinical manifestation, changed the statistical significance (20). As mentioned in the literature, internal carotid artery stenosis levels are reported by the observers with 5% inter-observer variability. In our study according to the first observer, the evaluated three vessel segment had stenosis levels of 69%, 68%, 69% respectively in TRICKS MRA in the stenosis range of 70-99% (fig 5). Thus, they were classified in the 50-69% stenosis rate. according to the second observer the evaluated 2 vessel segment had stenosis levels of 66%, 68% respectively in TRICKS MRA in the stenosis range of 70-99%, Thus they were classified in the 50-69% stenosis rate. As a result of this, 1-5% change in the measurements of stenosis grading affected the statistical analysis.

One of the major limitations of our study is that, stenosis measurements in TRICKS MRA were only taken via MIP images acquired from the sagittal planes; The measurements via DSA were performed in the lateral plane. Single plane measurement could result in misleading measurements. To increase the diagnostic accuracy, a volumetric measurement would be more ideal than measurement from a single plane.

Although our study is one of the largest series in literature comparing TRICKS MRA and DSA in the diagnosis of carotid artery stenosis, our statistical power is limited by the low sample group. In spite of this, our results shed light toward future directions.

TRICKS MRA is a safe technique without requiring the bolus test technique. It is not complicated by timing software. It improves the defining of complex morphology of the proximal internal carotid artery by slow bolus injection of contrast agent. When compared with MRA without contrast, TRICKS technique decreases artifacts and increases diagnostic reliability. Although the necessity of a technique such as DSA is emphasized as a reference in ongoing trials, early experiences show that TRICKS would gain a major role in the evaluation of carotid artery stenosis.

According to our results we believe that TRICKS MRA is a noninvasive and safe alternative to DSA in the diagnosis of ICA stenosis; however, given the importance of rate of stenosis and plaque surface properties in clinical decision making, DSA evaluation must be performed on patients for whom treatment is planned.

Conflict of interest disclosure

The authors declared no conflicts of interest

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