Clinical Research

Comparison of Different Quantitative Methods and Visual Evaluation on the Tc-99m-HMPAO Brain Perfusion SPET

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ABSTRACT

Objectives Brain perfusion SPECT has been widely used for evaluation of brain perfusion and metabolic status. We aimed to compare different quantitative methods on Tc-99m-HMPAO SPET based on visual evaluation.

Materials and Methods: Forty-seven patients were enrolled in this comparative study. Tc-99m-HMPAO brain SPET was performed. For semi-quantitative analysis, two orbitomeatal (OM) composite slices were obtained. Regional cerebral perfusion data were semi-quantitatively computed by the ratio between each cerebral ROI mean-counts and the reference region mean-counts. Mean counts of the cerebellum, mean-counts of lower OM slice and contralateral ROI mean-counts were used as reference regions. Two different nuclear physicians evaluated all images. It was considered 0 (=hypoperfusion area); 1 (=normal perfusion area) and 2 (=hyperperfusion area) by visual evaluation. SPET slice's region of interest (ROI) data were analyzed by receiver operator characteristics (ROC) method to establish the optimal decision threshold for different quantitative methods.

Results: Our results observed that usage of small ROIs were better than larger ones. The mean-counts of lower OM slice had a positive correlation with the cerebellum mean-count. Additionally, as reference regions, mean-counts of lower OM slice was slightly better than cerebellum and evidently better than symmetric region of the contralateral hemisphere.

Conclusion: We did not found the expected high correlation among visual analysis and these quantitative methods. We believe that new quantitative methods on the Tc-99m-HMPAO brain perfusion SPECT are required. ©2006, Fırat Üniversitesi, Tıp Fakültesi

Key words: Quantitative, brain, SPET, Tc-99m-HMPAO, roc analysis.

ÖZET

Tc-99m-HMPAO beyin perfüzyon SPET'inde farklı ölçüm metodları ve görsel değerlendirmenin karşılaştırılması

Amaç: Beyin perfüzyon sintigrafisi beyin perfüzyonu ve metabolik durumunu değerlendirmek için yaygın olarak kullanılmaktadır. Biz görsel değerlendirmeye dayanarak Tc-99m-HMPAO SPET'deki farklı ölçüm metodlarını karşılaştırmayı amaçladık.

Gereç ve Yöntem: Kıyaslamalı çalışmamıza 47 hasta dahil edildi. Tc-99m-HMPAO beyin perfüzyon SPET uygulandı. Yarı-kantitatif analiz için iki orbitomeatal (OM) compozit kesit oluşturuldu. Bölgesel serebral perfüzyon bilgileri semi-kantitatif olarak her bir serebral ROI ortalama sayımı ve referans bölge ortalama sayımı arası oran olarak hesaplandı. Serebellum sayım ortalaması, alt OM kesit sayım ortalaması ve karşı hemisfer ilgi alanı sayım ortalaması referans bölgeler olarak kullanıldı. İki nükleer tıp uzmanı bütün görüntüleri değerlendirdi. Görsel değerlendirmede ilgi alanlarını 0 (=hipoperfüze alan); 1 (=normal alan) ve 2 (=hiperperfüze alan) olarak tanımladı. SPET kesiti ilgi alanları bilgileri farklı ölçüm metotlarının ideal karar eşiğini temin metodu olan ROC analizle değerlendirildi.

Bulgular: Bizim bulgularımız küçük ilgi alanları almanın büyük ilgi alanlarından daha iyi olduğunu gösterdi. Alt OM kesit sayım ortalaması serebellum sayım ortalaması ile pozitif korelasyona sahipti. Ek olarak, referans alan olarak, alt OM kesit sayım ortalaması kullanımı serebellumunkinden hafif; karşı hemisfer simetrik alanınınkinden ise belirgin daha iyiydi.

Sonuç: Biz görsel değerlendirme ile bu ölçüm metotları arasında beklediğimiz yüksek uyumluluğu bulamadık. Beyin perfüzyon Tc-99m-HMPAO SPET te yeni ölçüm metotlarına ihtiyaç olduğunu düşünmekteyiz. ©2006, Fırat Üniversitesi, Tıp Fakültesi

Anahtar kelimeler: Kantitatif, beyin, spet, tc-99m-hmpao; roc analiz.

Brain perfusion SPECT has been widely used for evaluation of brain perfusion and metabolic status. This information is often complementary to the anatomic detail provided by structural neuroimaging techniques such as computerized tomography and magnetic resonance imaging (1).

Standardization techniques in quantitative evaluation of the cerebral perfusion SPECT require a number of control cases to be matched to the clinical studies, allowing for evaluation of a patient scan by comparison of the results with a reference database for diagnostic accuracy in cerebral disorders. Knowledge of the normal distribution of the radiopharmaceuticals in the brain is mandatory when estimating pathological alterations in rCBF (2).

For the planning of future quantization protocols, comparison of these methods are becoming ever more important to identify and characterize the "probable" changes in the regional cerebral blood flow (rCBF) distribution.

We aimed to compare different quantitative methods on Tc-99m-HMPAO SPET based on visual evaluation.

MATERIALS and METHODS

Forty-seven patients (15 female, 32 male, age range 20-82 y, mean 58.3 ± 15.5 y) were enrolled in this comparative study. Eleven patients were treated with extremity revascularization, replantation or amputation who treated in department of orthopedic and traumatology. Thirty-six patients had different

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stage Parkinson disease that were treated in department of neurology. Ethics Committees of our institution approved the study protocol and informed consent was obtained from each patient.

Radiopharmaceuticals and SPECT examination: The radiopharmaceuticals was prepared strictly according to the manufacture's instructions. Radiochemical purity exceeded 85% at the time of injection. For brain SPECT perfusion imaging, 740 MBq Tc-99m-HMPAO (Frederic Joliot-Curie National Research Institute, Budapest, Hungary) was injected intravenously in a tranquil place with eyes closed and ears occluded and dimmed light after about 30 min rest, within 15 min after placement of an intravenous line. Patients were examined in a supine position with a head holder to avoid motion artifact. Imaging was initiated approximately between 20 min to 90 min after injection. SPECT brain imaging was performed using a two-headed gamma camera (Adac vertex plus V-60) equipped with a high resolution low energy collimator. The projection data were acquired for 25 s per projection at 60 equal angles of a complete revolution (0-360). Data were obtained from the 140 KeV photo peak (20% window) and a 64 x 64 matrix and zoom factor of 1.85. Reconstruction was performed by filtered back-projection using a Gaussian filter (cut off frequency 0.38 cycle/cm, order 20) with attenuation correction by the Chang method. Slice thickness of SPECT samples was 6.3 mm. After reconstruction, orbitomeatal (OM) transaxial, coronal and sagittal images were obtained.

For semi-quantitative analysis of neuroanatomical region of interest, two OM composite slices were obtained. Lower OM transaxial composite slice was obtained by summing up the three consecutive well-seen basal ganglia and thalamus slices. Upper OM transaxial composite slices were obtained by summing up the two consecutive slices and distance to lower OM transaxial composite slice was 44.1mm (Fig. 1- 3).

Basal nucleus, thalamus and other cortical region's of interest (ROI) were drawn manually on the slices.

For visual interpretation, two different nuclear physicians evaluated all images. The images were viewed on a color monitor using a spectrum scale of 255 colors (thermal) and gray scale. All OM slices and two composite OM slices were displayed. Two experienced nuclear medicine physicians who were unaware of the patient's diagnosis visually assessed the SPET slices. Disagreement was resolved by discussion to reach a consensual interpretation. To facilitate determination of perfusion, all ROI's activity uptake was compared with general cortical uptake. If ROI contained decreased or increased perfusion area, it was considered 0 (=hypoperfusion area) and 2 (=hyperperfusion area). If ROI did not contain 0 or 2, it was considered 1 (=normal perfusion area).

On the semiquantitative evaluation, all ROI's were divided into two groups, large ROI's group and small ROI's group. Total frontal lobe, hemi-frontals, temporal lobes and hemi-occipitals on the lower OM composite slice (fig. 2) and right and left hemispheres on the upper OM composite slice (fig. 3) were drawn manually as large ROIs.

Semi-quantitative ROI count ratios were obtained by following formula:

$$\text{ROI count ratio} = \frac{\text{Mean-counts of ROI}}{\text{Mean-count of reference region}}$$

Cerebellum and lower OM slice (as a whole brain) and symmetric ROI on the contralateral hemispheres were used as reference regions.

Mean-count of the symmetric ROI on the contralateral hemisphere were used as a reference region, (<1) ratios were standardized by (1/ratio) value on the ROC analysis and symmetric hyperperfusion were considered as a normal perfusion in the visual evaluation.

SPET slices region of interest (ROI) data were analyzed by receiver operator characteristics (ROC) method to: establish the optimal decision threshold for different quantitative methods. Receiver-operating characteristics (ROC) curves and the area under the ROC curve (Az) were calculated. A maximum value of (specificity + sensitivity) was considered as a cutoff value for each quantitative method. The method, which had larger areas under curve and smaller statistical significant p value, was considered better.

The Pearson correlation test was used to examine the relationship between cerebellum and lower OM slice mean-counts.

The SPSS version 11.0 (SPSS Inc, Chicago, USA) was used for all statistical analyses. The level for statistical significance was set at p<0.05 for all test.

RESULTS

For evaluation of regional cerebral blood flow on the upper and lower OM slice, we found that usage of the small ROI were better than larger ones.

As a reference region, preference of the lower OM slice was slightly better than cerebellum and evidently better than symmetric ROI on the contralateral hemisphere for evaluation of hypoperfusion on the lower and upper OM slice (Table 1, 2).

The mean-count of lower OM slice had a positive correlation with the cerebellum mean-count (Pearson correlation test: r=0.874, P=0.001).
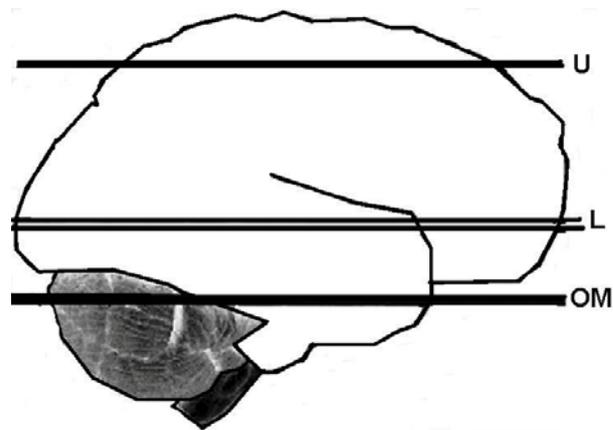

Figure 1. Orbitomeatal (OM) slices, upper (U) and lower (L) orbitomeatal slice.

Table 1. Lower OM slice ROC analysis results (R=Right; L= left; LOSAM= mean-counts of lower OM slice mean-count; SM= cerebellum mean-count and Az=Area under the curve).

Lower OM Slice	Hypoperfusion evaluation					Hyperperfusion evaluation				
	cutoff value	Positive	Negative	Az	P	cutoff value	Positive	Negative	Az	P
Total frontal/LOSAM	1.075	41	6	0.764	0.038	1.025	4	43	0.544	0.775
Total frontal/SM	3.057	41	6	0.659	0.214	3.190	4	43	0.802	0.047
Hemifrontal/LOSAM	0.945	88	6	0.906	0.001	1.035	7	87	0.598	0.391
Hemifrontal/SM	3.154	88	6	0.777	0.024	3.217	7	87	0.851	0.002
R/L hemifrontal	1.14	7	40	0.736	0.049	1.14	7	40	0.736	0.049
Small frontal/LOSAM	0.96	179	9	0.914	0.000	1.165	7	181	0.791	0.009
Small frontal's ROI/SM	3.020	179	9	0.868	0.000	3.682	7	181	0.909	0.000
R/L Small frontal's	1.2	10	84	0.744	0.012	1.2	10	84	0.744	0.012
Frontotemporal/LOSAM	0.925	86	8	0.958	0.000	1.015	6	88	0.608	0.378
Frontotemporal/SM	2.745	86	8	0.798	0.005	3.392	6	88	0.858	0.003
R/L frontotemporal	1.255	8	39	0.816	0.005	1.255	8	39	0.816	0.005
Temporal/LOSAM	0.985	81	13	0.703	0.019	1.025	6	88	0.554	0.659
Temporal/SM	2.760	81	13	0.620	0.166	3.248	6	88	0.837	0.006
R/L temporal	1.085	11	36	0.672	0.088	1.085	11	36	0.672	0.088
Small temporal/LOSAM	1.015	180	8	0.761	0.013	1.125	4	184	0.846	0.018
Small temporal/SM	2.777	180	8	0.569	0.511	4.04	4	184	0.808	0.035
R/L small temporal	1.138	12	82	0.683	0.041	1.138	12	82	0.683	0.041
Occipital/LOSAM		94	0			1.045	20	74	0.697	0.007
Occipital/SM		94	0			3.131	20	74	0.626	0.086
R/L occipital	1.105	2	45	0.467	0.874	1.105	2	45	0.467	0.874
Small occipital/LOSAM		188	0			1.135	27	161	0.846	0.000
Small occipital/SM		188	0			3.401	27	161	0.729	0.000
R/L small occipital	1.01	3	91	0.348	0.372	1.01	3	91	0.348	0.372
Basal ganglia/LOSAM	1.245	91	3	0.581	0.636	1.135	23	71	0.735	0.001
Basal ganglia/SM	3.391	91	3	0.678	0.297	3.18	23	71	0.521	0.762
R/L basal ganglia	1.02	14	33	0.502	0.981	1.02	14	33	0.502	0.981
Thalamus/LOSAM	1.065	77	17	0.742	0.002	1.225	8	86	0.626	0.241
Thalamus/SM	3.359	77	17	0.694	0.013	3.221	8	86	0.535	0.745
R/L thalamus	1.081	13	34	0.61	0.249	1.081	13	34	0.61	0.249

Table 2. Upper OM slice ROC analysis results (R=Right; L= left; LOSAM= mean-counts of lower OM slice mean-count; SM= cerebellum mean-count and Az = Area under the curve).

| Upper OM slices	Hypoperfusion evaluation					Hyperperfusion evaluation				
	cutoff value	Positive	Negative	Az	P	cutoff value	Positive	Negative	Az	P
R or L hemisphere/LOSAM	1.054	88	6	0.737	0.053	1.193	19	75	0.85	0.000
R or L hemisphere/SM	0.998	88	6	0.780	0.022	1.08	19	75	0.609	0.143
R / L hemisphere	1.086	5	42	0.893	0.004	1.086	5	42	0.893	0.004
Anterior four small ROI/LOSAM	1.15	185	3	0.805	0.07	1.26	19	169	0.844	0.000
Anterior four small ROI/SM	0.979	185	3	0.885	0.022	1.179	19	169	0.503	0.963
R/L anterior four small ROI	1.026	87	7	0.657	0.169	1.026	87	7	0.657	0.169
Posterior four small ROI/LOSAM	1.062	178	10	0.746	0.009	1.193	17	171	0.914	0.000
Posterior four small ROI/SM	0.915	178	10	0.830	0.000	1.038	17	171	0.687	0.011
R/L posterior four small ROI	1.135	84	10	0.458	0.668	1.135	84	10	0.458	0.668
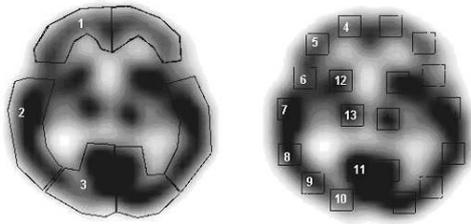
Figure 2. Lower OM composite slice: 1 (4 and 5), frontal; 2 (7 and 8), temporal; 3 (10 and 11), occipital; 6, frontotemporal; 9, temporooccipital.
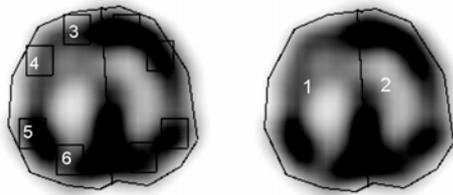

Figure 3. Upper OM slice: 1, right hemisphere; 2, left hemisphere; 3 and 4, frontal lobe; 5 and 6, parietal lobe

Symmetrical hyperperfusion was seen on 46 ROIs (8.3%) on the lower OM slice and on 23 ROIs (9.8%) on the upper OM slice. Symmetrical hypoperfusion was not seen.

Thalamic hyperperfusion and basal ganglia's hypoperfusion was not determined with these quantitative methods (p>0.05).

DISCUSSION

In brain perfusion scintigraphy, during semiquantitative evaluations shape of taken slices, drawing of ROIs and ratios used in quantization were not standardized. The shape, size and location of ROIs show considerable variability in different SPET studies. The ROIs, which we applied to OM transaxial slices, were similar to many authors' method or synthesis (3, 4).

Uptake counts of ROIs do not use direct quantification on Tc-99m-HMPAO cerebral perfusion SPET. ROI counts must be scaled to a reference region (mean-count of cerebellum, mean-count of whole brain or mean-count of the symmetric ROI on the contralateral hemisphere) (3- 5).

Soonawala et al reported that cerebellar normalization produces marginally more accurate diagnostic results in single-scan statistical parametric mapping analysis of Alzheimer-type disease patients than did mean-count of whole brain (5). In our

study, we found that mean-count of lower OM slice was slightly better than mean-count of cerebellum as a reference region.

Another comparison methods was an asymmetry index, [(right ROI − left ROI) x 0,5/ (right ROI + left ROI)] x 100, was calculated on SPET slices (2, 6). Asymmetry index is similar to our third method.

It appears that the assessment of rCBF varies depending on the radiopharmaceuticals used, the mean age of the investigated groups and the employed methodology. In addition, rCBF analysis has been carried out with different manual, semi-automatic and automatic methods for outlining the regions of interest, and the choice of method has also been shown to effect the results (2, 7, 8). One of the problems faced when attempting to properly map the CBF distribution is the large variety of regions under study hence the large number of anatomically defined functional variables obtained. The issue of how to deal with this statistical problem is still under discussion (9).

In same diseases, many studies showed that visually interpreted hypo or hyperperfusion areas were slightly or evidently different from statistically significant semi-quantitative analysis areas. For example, Chiu et al reported that abnormal hypoperfusion pattern was seen in 22 of 27 (82%) patient who had Tourette's syndrome. The involved area was the left frontal cortex (73%), left temporal cortex (50%), left basal ganglion (32%), right basal ganglion (9%), right temporal (4.5%) and left thalamus (4.5%). However, children with Tourette's syndrome had only a significant decreased perfusion in the left anterior temporal cortex with semi-quantitative analysis on the transverse images (3). This opposition between visual and semiquantitative evaluation may be related with complex organization of brain, hand dominance, hemispheric dominance, taken ROI areas or standardization methods, different somatotrophic reorganization or SPET acquisition and processing method (especially attenuation correction methods and back-projection filters).

Our study has three main limitations. First, visual assessment of abnormal cerebral uptake was often difficult in patients with mild reductions. Second, inter-observer variations may be larger in visual interpretation than quantitative evaluation. Three, as gold standard, quantization of the regional cerebral blood flow determined by PET can produce objective results and prevent these subjective errors.

Quantitative brain perfusion SPECT has been widely used for decrease of inter-observer variation and establishment of non visualized lesions. In our study, area under the ROC curve was evidently different among the quantization methods. Neither size of the ROIs nor preferred reference region was better in all brain regions for quantitative evaluation.

Conclusion: Our results established that using of the small ROIs was better than larger ones. The mean-counts of lower OM slice had a positive correlation with the cerebellum mean-count. Additionally, as reference regions, preference of lower OM slice was slightly better than cerebellum and evidently better than symmetric ROI on the contralateral hemisphere. Expected high correlation among visual analysis and the quantitative methods was not found. We believe that new quantization methods on the Tc-99m-HMPAO brain perfusion SPET are required.

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