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Review Article

SPECT Ioflupane123I (DaTscan), 99mTc (TRODAT) and Ioflupane with Myocardial Scintigraphy 123I (MIBG) for Diagnosis of Parkinson's Disease

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Abstract: Parkinson's disease (PD) is one of the most common neurological disorder diseases which takes place when brain cells gradually die. PD is considered a challengeable disease because of the similarities between PD and other brain disorders. For this reason, there are several ways to diagnose PD. Nuclear medicine can be a solution to distinguish the similarities between some brain disorders and PD. The aim of this review is to understand the differences between three radiopharmaceuticals used to diagnose PD and to list the advantages and disadvantages of using each radiopharmaceutical. This review includes studies from 2014 to 2019. Every study published before 2014 was excluded. The database used for this search was found in PubMed. English filters and best matches were used to minimize the outcomes. The comparison between PD nuclear medicine agents was established according to three main points: availability and the length of the scan, sensitivity and specificity, and visual evolution. It would appear that using TRODAT 99mTc can be helpful for some departments that other agents cannot offer, especially 123I. However, using MIBG as a biomarker increases the specificity in some studies. MIBG 123I can be used with TRODAT 99mTc as a biomarker. Moreover, applying PET/CT agents can be studied and researched along with nuclear medicine agents. More research studies are needed to understand the relation between cardiac uptake and PD.

Keywords: SPECT, Parkinson's Disease, TRODAT, DaTscan

1. Introduction

Parkinson's disease (PD) is one of the most common neurological disorder diseases which takes place when brain cells gradually die. PD is classified into two categories: motor and non-motor [1]. Furthermore, PD has widespread occurrences in the United States. There are about 50,000 patients diagnosed with PD annually [2]. However, diagnosing PD can be challenging because of the resemblance between PD and other neurological diseases [3].

Magnetic resonance imaging (MRI) plays a significant role when it comes to diagnosing PD. Also, MRI is considered superior in the case of soft tissue imaging.

Furthermore, nuclear medicine imaging includes ordinary nuclear medicine gamma camera single-photon emission computed tomography (SPECT) and positron emission tomography-computed tomography (PET/CT) which makes it possible to investigate the amount of dopamine transporter density in the striatum [4]. The presynaptic nerve carries the dopamine into vesicles. Dopamine is released from vesicles into the synapse and tags the predominantly postsynaptic dopamine receptors.

In addition, dopamine is transferred out of the synaptic cleft and stored in the nigrostriatal nerve terminals when it comes back from the synaptic cleft [5]. The use of dopamine is essential to PD detection because it controls movement, which is not only PD related, but also related to attention deficit

hyperactivity disorder [6].

Unfortunately, PD has symptoms and signs similar to other brain diseases. Nevertheless, even with the presence of SPECT imaging and dopamine transporter imaging, images can still provide positive results for PD, PD tremor dominant, idiopathic normal pressure hydrocephalus (iNPH), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), hemimoyamoya disease and post stroke tremor [7]. Ioflupane123I (DaTscan) (N--fluoropropyl- CIT; or FP-CIT), is commonly used in nuclear medicine departments for evolution PD and is established by using analogues of cocaine [8].

In Europe, Ioflupane123I has been available since 2000 and was approved in the United States by the Food and Drug Administration in 2011 [5]. Additionally, one of the first radiotracers found for imaging PD is 99mTc (TRODAT). TRODAT binds to the dopamine transporter and is a cocaine analog [9]. TRODAT is a Technetium-99m (99mTc), labeled the most available radiotracer. It has been used in nuclear medicine departments and is both inexpensive and quite safe to use [10].

2. Problem Statement

PD is considered a challengeable disease because of the similarities between PD and other brain disorders. For this reason, there are several ways to diagnose PD. Nuclear medicine can be a solution to distinguish the similarities between some brain disorders and PD. However, in nuclear medicine, there is more than one isotope, and radiopharmaceuticals have been used and selected, depending on the availability of the radiopharmaceuticals, the length of the scan, and sensitivity and specificity of the diagnosis PD. The review question will be: What are the differences between SPECT Ioflupane123I (DaTscan), 99mTc (TRODAT) and Ioflupane with Myocardial Scintigraphy 123I Metaiodobenzylguanidine (MIBG).

3. Aims

The aim of this review is to understand the differences between three radiopharmaceuticals in order to diagnose PD and to list the advantages and disadvantages of using each radiopharmaceutical. Additionally, a final aim of this review will be to discuss the overall results and determine the accuracy of each of these radiopharmaceuticals.

4. Methodology

This review includes studies from 2014 to 2019. Every study published before 2014 was excluded. The database used for this search was found in PubMed. English filters and best matches were used to minimize the outcomes. Also, two other databases that were added were Google Scholar and Ovid for accuracy purposes and to make sure all the studies were included in the review.

The following keywords were used to narrow the results:

SPECT Parkinson's Disease, SPECT, (Metaiodobenzylguanidine) MIBG in Parkinson's Disease,

TRODAT, Ioflupane, DaTscan. A total of 1406 searches were recorded as records identified through database searching. There was no other database used in this review. After filtering out duplicates, similar articles were excluded. The articles totaled 957. There were 880 articles screened according to title, abstract, method, and results. Seven hundred and fifty articles were excluded. Full-text articles assessed for eligibility amounted to 130. Some articles were excluded for the following reasons: sleeping disorders, funded articles, and articles based on animal research. There was a total of 13 articles, including studies.

5. Literature Review

5.1. Ioflupane123I (DaTscan) and 123 I MIBG Applications

In a prospective study obtained during 2016 from 24 patients, patients were subjected to both exams: DaTscan and MIBG. All the participants were sent by neurology specialists with PD or parkinsonian syndromes. There were 14 males and 10 females and the average age was 67.4 years. All patients were scanned within six months for both exams [7].

The main purpose of the Asahi et al. study is to understand the relationship between DaTscan and MIBG. The researchers believe that understanding this relationship will help improve the treatment through Deep Brain Stimulation (DBS). In this study, researchers collected the Specific Binding Ratios (SBRs) by using Datview software. The early and delayed responses of the Heart to Mediastinum Ratios (HMRs) were collected by using three different software programs.

According to Asahi et al., the critical component of the examination allows specialists to be able to establish a connection between PD and what it is called Scans Without Evidence of Dopaminergic Deficit (SWEDDs) [7]. The study addressed the false positive findings of the DaTscan and MIBG combining images. According to the findings, DaTscan provides positive results regarding PD, dementia with Lewy Bodies (DLBs), multiple sclerosis, progressive supranuclear palsy, and coticobasal degeneration.

Negative results were found for essential tremors and Alzheimer's dementia patients. On the other hand, MIBG showed true positive results in PD and DLBs, and negative results with the rest of non-Parkinson diseases [7].

In another prospective study, which took place in Japan, Uyama et al. introduced the biggest concern regarding PD, which is the misdiagnosis of PD with DLB's and another non-Parkinson's syndrome. The study concentrated on imaging PD with DaTscan and MIBG to confirm the results of the DaTscan [12]. Thirty-four patients were scanned with both DaTscan and MIBG during a four-month period.

The SBR was analyzed from the DaTscan images with the same software that had been used in the previous study with DaT view. However, MIBG images were acquired in both technique planar imaging and SPECT imaging and the HMR

was taken in the early and delayed uptake. Out of the thirty-four patients who were diagnosed with PD, only 15 patients confirmed the primary diagnosis. According to Uyama et al., the limitations were based on the size of the study's participants; the patients' histology was ignored and the medication that the patients took could affect MIBG results [11].

Yoshii, Ryo, Baba, Koide, & Hashimoto started their study by introducing MIBG methods as biomarkers of PD diagnosis. The study sample was based on eighty-four patients who were scanned between 2014 to 2016. Because of the accuracy of MIBG results, the study excluded patients with a history of diabetes, heart issues, family history of PD. The findings of both scans revealed 13 patients with PD, 19 non-PD syndromes, and four patients diagnosed with MSA [12].

MIBG images were taken early and delayed with an acquisition time of 360 seconds.

The early images were taken after 20 minutes from the injection and the delay images were taken after 4 hours. The researchers made sure all the patients who went under MIBG scan were not taking any heart medication. In addition, the patients were sent to take an ultrasound cardiograph to appraise the heart function.

On the other hand, DaTscan imaging time lasted six to ten minutes, according to the type of scanner, either dual head or triple head [12].

According to Yoshii et al., the study used the Bolt method and DAT view to analyze the SBR data. The results were divided in two groups. The first group was composed of patients with PD; the second group consisted of patients with CBC, PSP and MSA. The study used a Receiver Operator Characteristic (ROC) curve to create two groups of patients. There were also some limitations in the Yoshii et al., study.

The first limitation was a result of the research sample being small, as well as the time lapse between the initial scan and the follow-up scan [12].

5.2. Technetium-99m Labeled Tropane Derivative (99mTc-TRODAT-1) Applications

Technetium-99m labeled tropane derivative (99mTc-TRODAT-1) Applications A cross-sectional study was done among Brazil's PD patients and healthy patients. The study was based on scanning PD patients using Technetium -99m (99mTc) TRODAT. The total sample was taken from twenty patients. The TRODAT scan was preformed between January 2008 to December 2009. All patients stopped their antiparkinsonian medication for 12 hours before the scan. Four hours after the injection is the time between the scan time and the tracer administration.

Region of Interest (ROI) was drawn around caudate nucleus, striatum, occipital lobe and putamen. Occipital lobe is considered as reference to measure the brain background (non-specific DAT binding). Ferraz et al., used this formula to calculate the SBR (specific binding-nonspecific binding)/ nonspecific binding [13].

The findings for the Ferraz et al. cross-sectional study showed a decreased uptake in the striatum, caudate nucleus and putamen. The study mentioned the advantages of using TRODAT scan such as material availability and half-life. 99mTc is lower in price compared to iodine 123I.

Using positron emission tomography (PET) is superior in PD diagnosis because of the image quality, but it is also more expensive than DaTscan and TRODAT. Furthermore, PET scan has a lower availability than gamma camera. The Ferraz et al. conclusion addressed using TRODAT as a biomarker of PD diagnosis and differentiating it in healthy patients [13].

Other studies examined PD using TRODAT with eighty-three PD patients. There are four categories which were excluded from this study, such as secondary parkinsonism, sustained remission, pregnant patients, and inability to support SPECT/CT.

The dose for TRODAT was 20 to 25 mill curie (mCi) and the scan was performed after 3 hours from the tracer administration. Computed tomography was done for the attenuation correction. The PD diagnosis used the visual analysis since there was no SBR calculation mentioned in this study [14]. Mittal et al., concluded that TRODAT was able to diagnose or evaluate PD from PPS, but there were false negatives in some cases, especially regarding specific uptake ratios (SUR) and patients with (Hoehn and Yahr) H and Y staging [14].

In a prospective study done during the year 2017 on 15 patients between 36 years old to 82 years old, research by Sasannezhad et al., sought to distinguish the differences between early onset PD (EOPD) and late onset PD (LOPD) using TRODAT [15]. The imaging protocol for this study is four hours after injection of one bolus. The results for this scan were evaluated visually according to the uptake of the striatum. The study of Sasannezhad et al. evaluated three groups:

normal, absent, and decreased. According to the findings, there were no differences between EOPD and LOPD [16]. However, in their discussion, Sasannezhad et al. mentioned other studies done with same concept. The study showed EOPD has lower uptake than LOPD. In conclusion, Sasannezhad et al. confirmed the results, but there was uptake at the putamen [15].

5.3. Single Scan DaTscan 123I Applications

Using ioflupane-123 alone is one of the common scans used to diagnose PD. There are a lot of articles and studies that have been done on the administration of ioflupane-123. Kim, Wit, & Thurston have performed studies using DaTscan such as "Artificial intelligence in the Diagnosis of Parkinson's Disease from Ioflupane-123 Single-Photon Emission Computed Tomography Dopamine Transporter Scans Using Transfer Learning" [16].

The authors discussed the normal and abnormal appearance of DaTscan imaging. According to Kim et al., normal DaTscan is equilibrium uptake in the caudate nuclei, putamen and less uptake in the background of the brain [16].

In addition, putamen will appear as a comma shape. On the other hand, the abnormal DaTscan loses the comma shape or asymmetric uptake in the right or left putamen. Kim et al. used deep learning also known as Artificial Intelligence (AL)

concept with ioflupane-123 scan to improve the sensitivity and specificity. Their study showed increase of DaTscan results using AL [16].

6. Discussion

6.1. Techniques

Some nuclear medicine procedures require giving the patients medication to obtain correct scan and diagnosis. On the other hand, other nuclear medicine procedures require the patients to stop some medication because some of these medications can interfere with the results.

99mTc is one of the most common radiopharmaceuticals in nuclear medicine. In addition, 99mTc covers more than 85% of nuclear medicine applications.

The reasons for usage of 99mTc rather than other radiopharmaceuticals are the availability of 99mTc, the short half-life for the daughter (99mTc) and long half-life for the parent's molybdenum-99 (99Mo). Short half-life (six hours) is suitable for the patients, so the tracer will be cleared out of the patient's body faster and the long half-life (60 days) for 99Mo will to be able to elude the generator for a long time and produce99mTc.

The second reason is that 99mTc has a suitable energy that is perfect to work with, which is 140 kilo electron volts (keV) compared to other radioisotopes such as iodine-131 with energy 971 keV, iodine 35 keV and Indium with different peaks of energies [17]. In addition, radiopharmaceutical kits are available at any nuclear medicine department, and a nuclear medicine technologist can make the radiopharmaceuticals immediately without ordering special doses from the pharmacy.

This feature of making the radiopharmaceuticals at the nuclear medicine department allows the procedure to be available at any time of the day, especially for emergency cases. TRODAT 99mTc procedure involves easy instructions and does not require any medication, although the patient needs to stop any antiparkinsonian medication for 12 hours before the scan.

Most of the studies have been done using TRODAT 99mTc to harmonize the time between the intravenous injection and the scan, which is between three to four hours. Furthermore, the radiopharmaceutical dose is between 20 to 25 mCi of TRODAT 99mTc.

In addition, TRODAT 99mTc considers the first radiopharmaceutical based on 99mTc for imaging dopamine transports because of the outstanding binding to dopamine transports in the basal ganglia. TRODAT 99mTc can be produced with 90% radiochemical purity and even higher in a nuclear medicine department hot lab [18]. Ferraz HB., discusses a study which focuses on the four hours between the intravenous injection and the scan time of 814 megabecquerel (MBq), which is equal to 22 mCi [13]. However, filters were used in this study such as Butterworth low pass filter, and attenuation correction was applied, and fan beam collimators were used [14].

In the Sasannezhad et al. study, similar techniques were used for four hours after the injection and 740 MBq of TRODAT 99mTc were administered. In this article, the collimator was parallel to whole high resolution low energy (HRLE). In addition, TRODAT 99mTc scan time is 30 minutes which is 60 to 64 projects per three seconds at a 180 angle for dual head gamma camera.

However, the scan time will be shorter if triple head gamma camera is available [15]. As with any radiopharmaceutical based on sodium pertechnetate ($[TcO_4]^-$), it is possible to make TRODAT 99mTc at the hot lab by following these steps: 0.5 mL of saline 0.9% should be added to a TRODAT cold kit and kept at room temperature for five minutes without adding the radioactive.

After that, 30 to 40 mCi of $[TcO_4]$ will be withdrawn in the syringe with 1 mL saline and added to the TRODAT kit. The whole kit must be swirled and placed in the dry heater for 30 minutes at 95 C. Finally, the kit should be cooled down for 20 minutes. TRODAT 99mTc kit has around 40 mCi and this dose is adequate for two patients [19].

On the other hand, Sodium Iodide (123I) is a radioactive isotope produced in a cyclotron by proton irradiation of xenon, the opposite of 99mTc which is produced from 99Mo generator. 123I has a half-life of around 13 hours and peak energy of 159 KeV. This energy peak is close to 99mTc, which is 140 KeV.

DaTscan technique is different from that of TRODAT 99mTc because the main isotope is based on Iodide which is organified by the thyroid. For this reason, the patient needs to be given a thyroid blocker. The two most common thyroid blockers are Lugol, whose dose is 100 mg; the second blocker is potassium perchlorate at 500 mg. The most known protocol is administering the patient one hour before the scan [20] However, administrating thyroid blockers will extend the scan time for about 5 hours because of one hour for the thyroid blocker and from three to four hours after DaTscan injection.

In addition, and in some cases, the blocker will be administrated 24 hours before the scan and the scan time will take around 60 minutes [16]. Beside thyroid blockers, patients with high sensitivity to iodine are not eligible for DaTscan. However, according to Palumbo et al., and for other studies that were done using DaTscan and which were included in this review, the dose was around 3-5 mCi and the striata binding was between 3-6 hours [21]. However, according to sources such as "Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine" by Kowalsky & Falen, the technologist needs to inject 123I DaTscan over 15 to 20 seconds (slow injection). In addition, there is less than a 1% chance of getting a headache, nausea, pruritus, vertigo, xerostomia, and formication after the injection [20].

For these studies that address combining DaTscan and MIBG 123I scan, the part that is related to the DaTscan is the same as the regular protocol for PD; the only difference is in using MIBG as biomarkers for PD. 123I MIBG is a radiopharmaceutical used to image adrenal medulla and therapy on tumors from neural crest cells.

However, the relation between 123I- MIBG can be difficult to understand because the image will be taken for the chest and

HMR, between the heart and the mediastinum, and will be used to confirm DaTscan results. 123I MIBG is a technique that evaluates cardiac sympathetic functions and is considered an analog of norepinephrine that was developed as a sympathetic nerve imaging [22]. The issues with 123I MIBG are many, such as the relation between PD and the uptake in the heart, which are still not clear scientifically, even though the result of using MIBG increases the accuracy of diagnosis. In addition, and according to the studies that used MIBG, a heart disease is a contraindication for using MIBG as a biomarker.

However, 123I DaTscan requires at least ten half-lives to be cleared from the body and the department can inject 123I MIBG to confirm the DaTscan results. In addition, 123I MIBG will increase the total procedure time because the earliest is after 15 minutes from the injection and the delay image appears after three hours. Also, the scan time will be ten minutes for each image: the early and the delay.

However, MIBG will share the difficulty with DaTscan to prepare the dose at the hot lab.

There was no difference in total procedure time between the three radiopharmaceuticals even though DaTscan and MIBG required some additional steps such as using thyroid blockers.

However, some studies did not mention the scan time and the thyroid blocker waiting time; and they were estimated at 60 minutes for the thyroid blocker and 45 minutes for the scan time according nuclear medicine protocols.

Also, there was one study with an extreme time gap [16], because the thyroid blocker was given to the patient 24 hours before the scan. In addition, in all the studies, the thyroid blockers were not mentioned for the MIBG and it is important for the scan because MIBG is based on 123I.

For this reason, the time of the thyroid blockers for MIBG was not included. As was mentioned in the introduction, PD will affect the patient's movements. In this case, the patient cannot tolerate the waiting time between the thyroid blockers and the intravenous injection and the scan time.

6.2. Sensitivity & Specificity

Sensitivity is a medical term used to measure how the test can detect a positive result; on the other hand, specificity means the ability to detect a negative result.

However, in between these concepts are also false-negatives and a false-positives. From table 1, TRODAT 99mTc has an acceptable sensitivity results in three studies 96%, 100%, and 92% and specificity 78%, 89% and 70%. Nevertheless, the patient's number and the selection criteria can affect these results. On the other hand, sensitivity and specificity results using DaTscan were not available in two studies.

The only study that mentions sensitivity and specificity was done by Kim et al., and the results for sensitivity and specificity were 96% and 66% respectively [16]. In this study, the specificity was high because the patient number was 54 [16]. Using MIBG as a biomarker with DaTscan did not improve the sensitivity but there was improved specificity in some studies Table 1.

Table 1. *Characteristics of studies and patients enrolled from studies.*

Study	Criteria Selection	Number of Patients	Age of Patient	Gender of Patient M/F	Radiopharmaceuticals
Mittal et al. 2018	IPD 43 PPS 15 HV 25	58	PD 54.7 ± 13.5 PPS 63.4 ± 7.2	PD 33/10 PPS 10/5	TRODAT ^{99m}Tc
Bor-Seng-Shu et al. 2014	PD 20	20	PD 43 to 76	PD 13/7	TRODAT 99mTc
Kim et al. 2018	Normal 54 Abnormal 54	118	NR	NR	DaTscan 123- I
Yoshii, Ryo, Baba, Koide, & Hashimoto 2017	120	120	47 to 89	61/59	DaTscan 123- I & MIBG 123-I
Uyama et al. 2017	34	34	31 to 81	19/15	DaTscan 123- I & MIBG 123-I

Table 1. *Continued.*

Study	Reference diagnostic stander	Total Exam Time	Methods Used to Judge SPECT	Sensitivity	Specificity	Accuracy
Mittal et al. 2018	UK Parkinson's Disease Society	AIW 3-4h SC 30 MIN	Visually & Quantitative (SUR) Software SPSS	96%	78%	NR
Bor-Seng-Shu et al. 2014	North American, Asian and European	AIW 4h SC NR	Quantitative (SUR)	100%	89%	NR
Kim et al. 2018	Royal Devon and Exeter Hospital UK	Thyroid Blocker 24H AIW 3.5 SC 60 min	Visually & Quantitative AUC	96%	66%	NR
Yoshii, Ryo, Baba, Koide, & Hashimoto 2017	Department of Neurology and the University of Oiso, Japan	DaTscan AIW 3H SC 30 min MIBG 15 min and 3 h	SBR and HMRs	DaTscan 91.7% MIBG 78.3% Combined 74%	DaTscan 15% MIBG 90% Combined 95	NR
Uyama et al. 2017	European Association of Nuclear Medicine	DaTscan time SC 28 min MIBG 15 min 3 h	SBR and HMRs	DaTscan 86.7% MIBG 93% Combined 86.7%	DaTscan 152.6% MIBG 47% Combined 37.7%	DaTscan 67.6% MIBG 67.6 Combined 79.4%

*IPD: Idiopathic Parkinson Disease, PPS: Parkinson Plus Syndromes, HV: Healthy Volunteers, PD: Parkinson Disease, AIW: After Injection Waiting, SC: Total Scan Time, SUR: Specific Uptake Ratios, SPSS: Statistical

*Package for the Social Sciences, NR: Not Reported, AUC: Area Under the Receiver-Operator Curve, SBR: Specific Binding Ration, HMR: Heart to Mediastinum Ratio

6.3. Visual Evolution

It is important to image the location and the concentration of dopamine transporters. The basal ganglia will show up as comma shape and symmetrical striatum on both sides. In Mittal et al., there is normal uptake with symmetrical striatum on one side and with abnormal striatum on the other side. [14, 15, 19] In addition, TRODAT 99mTc can evaluate the SBR as well as DaTscan, which can show the striatum and SBR [16, 23]. However, one of the limitations mentioned in the studies using these agents is that PD has identical results with other neurological disorders. When combining DaTscan and MIBG 123, the results can limit the other neurological disorders [6, 24].

On the other hand, there are some biomarkers that can be used as confirmation results, such as functional magnetic resonance imaging (fMRI) and Neuropsychiatric Inventory. The limitations of this study are that the number of patients in most studies is small, which can affect the outcome of the studies. In addition, the location of most of the studies was restricted to two or three countries. There were no studies that compared between the agents, especially DaTscan and TRODAT.

Also, another limitation was that some studies did not mention the protocol or did not mention the medication that was given to the patients, affecting, therefore, any possible comparison in gray areas, especially when the total scan time was involved. There were biomarkers involved in some studies which could affect the sensitivity results.

7. Conclusion

The comparison between PD nuclear medicine agents was based on three points. The first point is the availability and making the kit in the hot lab. It seems using TRODAT 99mTc can provide availability for some departments that other agents cannot offer, especially 123I. The second point involves comparing sensitivity and specificity according to this review. Overall, there was no immense difference between the three agents. However, using MIBG as a biomarker increases the specificity in some studies. In addition, DaTscan has commonly been used in nuclear medicine. In addition, using some software analyses improved PD evaluation and diagnosis such as surface fitting and Artificial Intelligence.

Recommendations are that more research of imaging PD on larger samples are needed. Also, MIBG 123I can be used with TRODAT 99mTc as a biomarker. Moreover, applying PET/CT agents can be studied and researched along with nuclear medicine agents. More research studies are needed to understand the relation between cardiac uptake and PD.

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