How to inject ictal SPECT? From manual to automated injection

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\begin{abstract}
Successful surgery depends on the accurate localization of epileptogenic zone before surgery. Ictal SPECT is the only imaging modality that allows identification of the ictal onset zone by measuring the regional cerebral blood flow at the time of injection. The main limitation of ictal SPECT in epilepsy is the complex methodology of the tracer injection during a seizure. To overcome this limitation, we present the main features of the first automated injector for ictal SPECT (epijet, LemerPax; La Chapelle-sur-Erdre; France). In this study we compared traditional manual injection with automated injection for ictal SPECT in 122 patients with drug-resistant epilepsy.

Methods: The study included 55 consecutive prospective patients with drug-resistant epilepsy undergoing injection with the automated injector. The control group was our retrospective database of a historic pool of 67 patients, injected manually from 2014 to 2016. Calculated annual exposure/radioactive dose for operators was measured. Injection time, seizure focus localization with ictal SPECT, as well as repeated hospitalizations related to inconclusive findings of the SPECT were compared in these two groups of patients.

Results: There were no differences in the average injection time with epijet (13 s) compared with the traditional manual injection (14 s). The seizure focus was successfully localized with ictal SPECT with epijet in 44/55 (80 %) patients and with manual injection in 46/67 (68 %) patients (p = 0.097). Repeated studies were required in 9/67 (23 %) patients in the manual injection group compared to 3 patients (7 %) in the epijet group (p = 0.141). Calculated annual exposure/dose for operators of 0.39 mSv/year and administered dose error inferior to 5 % are other advantages of epijet.

Conclusion: The first results using epijet are promising in adjustment of the injection dose, reducing the rate of radiation exposure for patients and nurses, maintaining the same injection time and allowing high SPECT accuracy. These preliminary results support the use of an automated injection system to inject radioactive ictal SPECT doses in epilepsy units.
\end{abstract}

1. Introduction

Patients with medically intractable seizures may be evaluated in an epilepsy unit for presurgical evaluation and successful surgery depends on accurate localization of epileptogenic zone (EZ) before surgery. Ictal SPECT is the only imaging modality that allows identification of the ictal onset zone by measuring the regional cerebral blood flow at the time of radiotracer injection (Grünwald et al., 1991; Newton et al., 1994; Rowe et al., 1989). Increased perfusion is expected within that seizure onset zone (SOZ) if the injection occurs before seizure propagation. Previous studies including metaanalysis demonstrated that Subtraction ictal-interictal SPECT co-registered to magnetic resonance imaging

\textbf{Abbreviations:} EZ, epileptogenic zone; SOZ, seizure onset zone; SISCOM, Subtraction ictal-interictal SPECT co-registered to magnetic resonance imaging; Tc-99m, Technetium-99m; HMPAO, Hexamethylpropyleneamine-oxime; TS, time of seizure identification; T\textsubscript{pump}, time required by the operator or the pump to inject; T\textsubscript{i}, total injection time; MBq, megabecquerel; Sv, sievert.

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(SISCOM) had the highest sensitivity among imaging modalities in identifying the epileptogenic zone in both temporal lobe (90 %–100 %) and extratemporal lobe epilepsy (81 %) (Spencer, 1994; Devous et al., 1998; O’Brien et al., 1998a).

The main limitation of ictal SPECT is that the radiotracer dose has to be calculated and administered manually, being a time-consuming process that requires the constant availability of trained medical staff at bedside for extended periods. As seizure onset is unpredictable, a tracer-filled syringe must be maintained close to the patient’s bed, waiting for a seizure to occur. The urgency of calculating the correct radioactive dose and rapidly administering it to a patient in the middle of an epileptic attack is stressful, with a subsequently higher dispensation dose error that may even increase the risk of radioactive contamination. Another limitation of manual injection is the delay in time between seizure onset and injection time. A time delay may occur during seizure identification, the time required to open the lead-shielded radiotracer box, removal of the syringe and flushing the fluid into the intravenous line, and measuring the volume to inject depending on the radioactive decay. Delayed injection from seizure onset increases the possibility of ictal activity propagation though the neurological network, making localization of the seizure focus with SPECT more difficult.

As a consequence of the complex methodology of ictal SPECT injection, this imaging procedure is not routinely available in clinical practice in the majority of epilepsy units. More recently, some studies have demonstrated that an automated injection system can overcome the main limitations of manual injections in ictal SPECT. Some epilepsy units have developed their own injection systems (Septuky et al., 1998; Van Paesschen et al., 2000; Setoain et al., 2012) or commercially available injectors of radiological contrast that has been re-adapted to inject radioactive doses (Feichtinger et al., 2007; Kim et al., 2013; Crawford et al., 2014). However, no dedicated commercially manufactured injection system for ictal SPECT is currently available.

In this study we present the main features of the first commercially available dedicated automated injector for ictal SPECT (epijet, Lem-Pax; La Chapelle-sur-Erdre; France) for use in patients with refractory epilepsy. Calculated annual exposure/radioactive dose for operators was analyzed. Injection time, seizure focus localization and repeated hospitalizations using epijet were compared with a retrospective database of patients injected manually.

2. Material and methods

2.1. Epijet

Epijet is a (CE label) medical device that automatically calculates the volume and injects a radioactive brain perfusion agent to locate the epileptic focus during patient seizure. Epijet is an injection system consisting of four modules: a front control module, a remote control module, an injection system module and a radio-protected fluid module described in Fig. 1.

![Fig. 1. Epijet system consisting of four modules:](image)

**a.** The front Control Module contains the injection buttons and the interface for prescription data. The parameters required to calculate the dose injected with decay time are: the radiotracer (HMPAO or ECD), prescribed dose, activity in the syringe and time of preparation. The system guarantees an error of less than 5% in prescribed dose administration.

**b.** The remote control module facilities injection made from the control EEG room. It includes a visual display of the status of the machine and injection buttons. Parameters presented on the screen during the waiting time are: remaining activity in the syringe and time to expiration.

**c.** The injection system module consists of two masses that press the plugs of two syringes.

**d.** The radio protected fluid module is a lead shielded cartridge that contains two syringes, one manifold and one pressure extension line. This closed kit has the following functions: protect the syringes with the perfusion radioactive tracer and saline; allows safe transport of the syringes from the radiopharmaceutical unit to the epilepsy unit; and finally, once adjusted in epijet, it connect the masses of the injection system with the syringes and then with a vein in the patient’s forearm through an extension line.

2.2. Patients

The study included 122 patients with drug-resistant focal seizures in presurgical evaluation undergoing ictal and interictal SPECT, video-EEG monitoring and MRI. Patients were stratified into 2 groups according to the different ictal SPECT injection modality performed.
The epijet group consisted of 59 consecutive prospective patients in whom tracer injection for ictal SPECT was performed with an automated injector. Four patients injected in non-ictal situations (syncope in two cases, nausea and eruct) were excluded. Therefore, 55 patients with a mean age of 36 years (31 males and 24 females) were finally included in this group.

The manual injection group consisted of our retrospective database of a historic pool of 67 patients in whom tracer injection for ictal SPECT was injected manually from 2014 to 2016. The patients had a mean age of 36 years, and 25 were males and 42 females.

Cases with inconclusive findings in the SPECT were sometimes rehospitalized to repeat ictal SPECT. The main reasons for SPECT repetition were non-matched SPECT images with EEG or with structural images, negative SISCOM, bilateral findings or late injection. These cases in the historic manual group were recorded and compared with the repeated cases in the epijet group.

All patients signed an informed consent form. The Ethical Committee of our hospital approved the use of the CE label epijet in patients.

2.3. Video-EEG monitoring and seizure focus localization

Video-EEG monitoring was performed using Nicolet BMSI 5000 equipment with 64 channels during one week (American EEG Society Guidelines, 1986). The definition of epileptogenic zone (EZ) was made by consensus in the epilepsy unit by means of conventional diagnostic methods that include video-EEG, MRI, clinical and neuropsychological data in all patients, as well as positron emission tomography (PET) in 67/122 cases. In the historic retrospective control group, the seizure focus was surgically removed in 26/67 patients and follow-up confirmed the EZ of these patients.

2.4. Tracer injection for ictal SPECT

The prescribed dose of Tc-99m Hexamethylpropyleneamine-oxime (HMPAO) was 925 MBq for both, manual or automated injections. Manual and automated injections were performed and analyzed by the same medical and technical staff.

For manual injections, a syringe filled with 1665 MBq in 7 mL of stabilized Tc-99 m HMPAO was stored in a lead container beside the patient’s bed and connected with an extension line prepared for intravenous injection into a vein in the patient’s forearm (Cereteq Estabilizado, 2002). Manual injection of the ictal SPECT was performed by an experienced operator, who was waiting for a seizure to start inside the patient room. When the seizure is detected, the operator presses the syringe mass and injects a volume of 4 mL, if seizure occurs within the first 2 h after tracer preparation. If the seizure occurs between 2 and 4 h after tracer preparation, 7 mL are injected. This injected volume guarantees a dose of between 820 and 1042 MBq of Tc-99 m HMPAO. Flushing the extension line with saline was never done because with the manual injection method, changing the syringe to flush the extension line produces a second bolus of Tc-99 m HMPAO with the activity remaining retained in the extension line. This may result in a second focus of uptake in the ictal SPECT. To avoid this second focus of uptake, flushing was not done in manual injections, so the injection line remains full of Tc99 m-HMPAO after the injection.

For automated injections, the kit contains 8 mL of the perfusion tracer of Tc-99 m HMPAO with 1665 MBq and normal saline to wash Tc-99 m from the extension line. In this case, the operator awaited the seizure from the EEG control room, outside the patient room. When a clinical seizure is detected, the buttons on the remote-control module are pressed. The system continuously calculates the remaining activity to inject the prescribed dose of 925 MBq until expiration of the tracer selected. With the automated injection there is no time lapse between Tc-99 m HMPAO and saline injection, which means that there is not a second bolus but rather a continuous injection.

2.5. Injection time

Seizure onset was defined as the time of earliest indication of auras or the beginning of rhythmic ictal discharge in the video-EEG. The time, taken by the EEG-technician, between seizure onset and the order to start injection is the time of seizure identification (Tsi) and is obtained by reviewing the video-EEG data. Tpump is the time required by the operator to perform manual injections of the tracer volume or the pump to do so in epijet injections. Epijet software records Tpump of each patient in a USB memory stick. The total injection time (Tj) is the time from seizure onset to the end of injection; Tj = Tsi + Tpump. Fig. 3A clearly differentiates the Tsi and Tpump of each patient in the epijet group. In the manual group (Fig. 3B) the video-EEG review does not allow differentiation between Tsi and Tpump, so Tj include in the same color bar Tsi and Tpump. The manual Tpump is the time that it takes the nurse to press the plunger of the syringe, which is no more than one or two seconds, and is very constant and almost insignificant, and has been included in the Tj.

2.6. SPECT acquisition and analysis

Ictal and interictal studies were acquired following the same protocol using a dual-head SPECT imaging system (Infinia, Hawkeye4™ 4; GE Healthcare Milwaukee, WI, USA). To assess and accurately locate the EZ before surgery, we used the SISCOM procedure (Subtraction Ictal Spect Co-registered to Magnetic Resonance Imaging) (O’Brien et al., 1998; Ros et al., 1999; Martí Fuster et al., 2013).

Ictal SPECT and SISCOM images were analysed by two experienced physicians who were blind to the clinical and radiological findings. SPECT localized the SOZ when an increase of perfusion in the ictal SPECT images was confirmed by the SISCOM images. SISCOM SOZ findings were compared with the EZ as determined by conventional diagnostic methods. Successful identification of the EZ must match SISCOM SOZ findings with the known EZ location at a sublobar level of accuracy; hence simply lobar concordance was considered as unsuccessful localization. When SISCOM was normal or failed to identify the SOZ compared with conventional diagnostic methods, the study was considered unsuccessful.

2.7. Radiation exposure

The dose rate at 50 cm from the surface of the syringe container was measured by an ion chamber radiation detector (Victoreen 451P-DE-SI-RYR, Fluke Biomedical, USA), and annual operator dosimetry was estimated for a standard working period.

2.8. Statistical analysis

To compare Tj with manual injection and with automated injection (unilateral hypothesis) a Student’s t-test for independent samples was used and p values ≤ 0.05 were considered as significant. The Chi square test was used for comparison of clinical data among the two groups, as well as for other parameters such as, successful and unsuccessful localization of the seizure focus with SPECT and the number of patients who had repeated studies among the groups.

3. Results

3.1. Patients

The most relevant clinical data, MRI findings and clinical seizure focus localization between the epijet group and manual injection group are summarized in Table 1. There were no statistical differences in the clinical data among the two groups in age, temporal vs extratemporal epilepsy, as well as MRI lesional versus non lesion epilepsy. Statistically significant differences were only seen in sex, with females being predominant in the manual injection group.
3.3. Seizure focus localization

The SOZ was successfully localized in 80% (44/55) patients undergoing ictal SPECT with epijet and in 68% (46/67) patients undergoing manual injection (Table 2). Although there were no statistically significant differences in SOZ localization between manual injection and epijet injection (p = 0.097), these results showed a trend towards statistical significance.

In the manual injection group there were 13% (9/67) repeated studies while in the epijet group 5% (3/55) of patients required repeat studies and were re-hospitalized to undergo ictal SPECT (Table 2). Using the Chi-square test, statistically significant difference was not detected in the number of repeated studies among the groups (p = 0.141). However, if we analyze these findings in greater detail, SPECT repetition was more frequent in the manual injection group in cases with negative or bilateral SISCOM, in non-matched results between SISCOM and v-EEG and, in one case of late injection (Fig. 3B; patient 3; injected 39 s. after seizure onset).

3.4. Dosimetry and radioprotection

The closed kit containing the perfusion tracer is shielded with 4 mm of lead. Radiation exposure at 50 cm with a syringe filled with 3700 MBq of Tc-99m inside the shielded cartridge was 0.07 μSv/h, and the calculated annual exposure/dose was 0.39 mSv/y, thereby demonstrating that the radiation levels were the same as the background radiation with optimal device functioning, according to the principles of radiation protection.

In the manual injection, the technician remains inside the patient room for long periods of time waiting for the seizure and, to inject the radioactive dose, he has to open the shielded box, take the shielded syringe with his hand and press the plunger of the syringe.

4. Discussion

In collaboration with the company Lemerpax, our Epilepsy Unit has developed the first dedicated commercially available automated injector system approved by the CE label. Epijet is based on a previous prototype by our group described by (Setoain et al., 2012). Epijet, however, has overcome some limitations detected in the first prototype. The main limitation was the long time necessary for the pump to inject the volume. The injection speed with epijet has now been increased at a rate of 2.0 mL/s, ensuring an injection time of less than 6 s.

Another important improvement was the radioprotected fluid module of epijet. The kit is prepared in the radiopharmaceutical unit and transported to the Epilepsy Unit in a closed cartridge. In this way, the perfusion tracer is not manipulated in the Epilepsy Unit, thereby avoiding possible contamination with radioactive material. Moreover, the 4 mm lead shielded cartridge reduces radioactive exposure to EEG technicians. In fact, the level of radiation exposure of 0.39 mSv/y that may be received with epijet is clearly well below the dose limits according to the Council Directive 2013/59/EURATOM, of 5 of December 2013 for occupational exposure (not exceeding 20 mSv/y) and for members of the public (not exceeding 1 mSv/y) (Torresin et al., 2019).

The remote control system of epijet was very useful and well accepted by the nurses and EEG technologists of our Epilepsy Unit. Von Hofen et al., have reported that an automated system improved the care of patients undergoing SOZ localization procedures as well as that of other patients in the Epilepsy Unit (VonHofen et al., 2012). The remote control system guarantees a more comfortable stay respecting patient privacy, without the presence of an EEG technician inside their room during long periods of time. This work also concluded that the automated injection system reduces nursing hours per patient and was thus, cost-effective. This is because one EEG technologist is sufficient to monitor different patients and simultaneously inject the tracer with the remote control system from the control room.
As demonstrated in a previous study (Setoain et al., 2012), the dose injected with manual injection is highly variable and depends on the time at which the injection takes place. To compensate for radioactive decay of Tc-99m during manual injection, the volume is readjusted once during the 4-h period. With this readjustment, the theoretic error between programmed and injected dose with manual injections may be greater than 12%. On the other hand, epijet guarantees the injection of 925 MBq with an average dispensation inaccuracy of less than 5%. The average TI using epijet (13 s) was not delayed or enlarged compared with manual injection (14 s). These results may be explained by the fact that the manual TI in our sample was very short (average of 14 s), thanks to the experience of our technicians in the injection of radiotracers under these conditions. Although TI was not decreased with epijet, the TI with epijet was more homogeneous, with lower SD and without late injections (SD of 6 s. and late TI of 27 s. with epijet instead of SD of 9 s. and late TI of 39 s. with manual injection), as shown in the box plot of Fig. 2 and in the individual TI of Fig. 3.

On the other side, manual injections have too many technical inconveniences compared with the more comfortable injections of the epijet group, which are injected from the control room with the remote control system.

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As explained previously, any delay between seizure onset and tracer

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**Table 2**

| Successful seizure focus localization | Epijet group | Manual group | p Value$^a$ |
|---------------------------------------|-------------|-------------|-------------|
| 44/55 (80%)                           | 46/67 (68%) |             | 0.097       |

| Unsuccessful seizure focus localization | Epijet group | Manual group | p Value$^a$ |
|------------------------------------------|-------------|-------------|-------------|
| 11/55                                   | 21/67       |             | 0.097       |

| Re-hospitalization to repeat ictal SPECT | Epijet group | Manual group | p Value$^a$ |
|------------------------------------------|-------------|-------------|-------------|
| 3/55 (5%)                                | 9/67 (13%)  |             | 0.141       |

**Causes to repeat ictal SPECT:**
- Non-matched with EEG
- Non-matched with structural lesion
- Bilateral activity
- Negative SISCOM
- Late injection

$^a$ Chi square test.
injection can seriously compromise results giving false readings caused by the spread of radioactivity (Setoain et al., 1998; Dupont et al., 2009). While in our series epijet did not modify T

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\textit{Submission declaration and verification}

Informed consent was obtained from all individual participants included in the study.

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\textit{Declaration of Competing Interest}

The first author Xavier Setoain has royalties related with sales of epijet.

The other collaborators members of the manuscript declares that they have no conflict of interest.

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\textit{Ethical approval}

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study has been approved by the Comité Ético de Investigación Clínica del Hospital Clínica de Barcelona. Register number: HCB/2016/0170.

Informal consent was obtained from all individual participants included in the study.

Epijet has been approved by the CE label in 2016 and is currently under review by the FDA.

\textit{Submission declaration and verification}

The authors declare that this work has not been published previously.

5. Conclusions

Epijet showed a very high rate of seizure focus localization allowing high ictal SPECT accuracy without loss of injection time compared with manual injection. The practical advantages of the automated injection system are promising in the adjustment of the injection dose and for avoiding radiation exposure, and the remote-control system allows patient monitoring by only one EEG technician and simultaneous injection of ictal SPECT tracers from the control room, thereby being cost-effective.

All these advantages in ictal SPECT injection methodology may justify the use of an automated injection system instead of traditional manual injection. A commercially available ictal SPECT injection system would help extend the use of ictal SPECT to more nuclear medicine departments.