

RESEARCH ARTICLE

Production of ^{68}Ga -citrate Based on a SnO_2 Generator for Short-Term Turpentine Oil-Induced Inflammation Imaging in Rats

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Abstract: Introduction: Gallium-68 citrate has been successfully applied in the PET imaging of infections and inflammation in some centers; however further evaluation of the tracer in inflammation models is of great importance.

Methods: ^{68}Ga -citrate prepared from [^{68}Ga]GaCl₃ (eluted from an SnO_2 based $^{68}\text{Ge}/^{68}\text{Ga}$ generator) and sodium citrate at optimized conditions followed by quality control tests was injected to normal and turpentine-oil induced rats PET/CT imaging studies up to 290 min.

Results: ^{68}Ga -citrate was prepared with acceptable radiochemical purity (>99% ITLC, >99% HPLC), specific activity (28-30 GBq/mM), chemical purity (Sn, Fe <0.3 ppm; Zn <0.2 ppm) in 15 min at 50°C. PET/CT imaging of the tracer demonstrated early detection of inflamed site in animal models in 60-80 min.

Conclusion: This study demonstrated possible early detection of inflammation foci *in vivo* using ^{68}Ga -citrate prepared using commercially available $^{68}\text{Ge}/^{68}\text{Ga}$ generators for PET imaging.

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INTRODUCTION

The interesting physical properties and availability of gallium-68 as a generator make it an interesting nuclide for developing new PET tracers.

[1]. The increasing trend in the production and use of PET radionuclides in nuclear medicine has offered new opportunities for researchers to focus on the production of new Ga-68 radiopharmaceuticals due to the availability and commercialization of Ge-68/Ga-68 generators.

Germanium-68 decays by pure electron capture (EC) to the ground state of ^{68}Ga with a half-life of 270.95 d [2]. Gallium-68 in turn decays with a half-life of 67.71(9) min by a combination of EC and positron emission primarily to the ground state of ^{68}Zn , but also with a branch to an excited state at 1077 keV with a probability of about 3% and a number of higher excited states with a combined probability of under 0.4 %.

^{67}Ga -citrate has been known as an infection/inflammation imaging agent for decades [3] and its production, quality control as well as its value in the evaluation of various infec-

tions has been reported [4]. After development of Ga-68 generators the first impression for development of Ga-68 citrate was not interesting since most of ^{67}Ga images were taken far beyond Ga-68 physical half-life, thus for some time the production and application of ^{68}Ga -citrate was ignored. However after implementation of few clinical trials in various centers interests began for ^{68}Ga -infection studies. The preliminary data confirmed a possible role for ^{68}Ga -citrate in the diagnosis of bone infections [5]. These reports initiated various animal studies in infectious animals as well as reporting production routes [6-9] and also some groups demonstrated the application of the tracer in atherosclerotic plaques in animal models as inflammatory applications [10] and also some reports on inflamed rabbit models [11], yet not much data and studies have been reported for the evaluation of inflammation in animal models for determination imaging time as well as other factors.

The area of research now is open for clinical researchers for the evaluation of this tracer in already-confirmed applications of its SPECT homolog, *i.e.* ^{67}Ga -citrate such as fever of unknown origin (FUO), severe lymphocytic inflammation, autoimmune-based inflammations or chronic pancreatitis, idiopathic pulmonary fibrosis, pulmonary Wegener's granulomatosis, Chronic bronchial asthma, sarcoidosis *etc.* [12]. On the other hand, the short half-life of ^{68}Ga -citrate, although considered an advantage from a dosimetric point of view was also a drawback at the same time because it did not

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allow the long uptake time typical of ^{67}Ga -citrate scintigraphy.

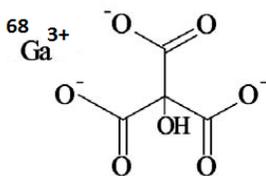


Fig. (1). Chemical structure of ^{68}Ga -citrate.

In this study we report, development of an in-house made the first generator, quality assurance and quality control of eluted $^{68}\text{GaCl}_3$ as well as a simple ^{68}Ga -citrate production method for any stand-alone PET center utilizing a Ga-68 generator. The preclinical evaluation the ^{68}Ga -citrate complex in wild type rats is also reported (Fig. 1).

METHODS

The prototype $^{68}\text{Ge}/^{68}\text{Ga}$ generator (50 mCi/day activity) was purchased from *Pars Isotope Co. Karaj, Iran*. Chemicals were purchased from the Aldrich chemical Co. (Germany). Normal saline, sodium citrate, acetone and sodium acetate used for radiolabeling were of high purity and had been filtered through 0.22 μm Cativex filters. Instant thin layer chromatography (ITLC) was performed by counting Whatman No. 2 papers using a thin layer chromatography scanner, Bioscan AR2000, Bioscan Europe Ltd. (France). Analytical high-performance liquid chromatography (HPLC), used to determine the specific activity, was performed by a Shimadzu LC-10AT, armed with two detector systems, a flow scintillation analyzer (Packard-150 TR), and UV-Visible (Shimadzu) using a Whatman Partisphere C-18 column 250 \times 4.6 mm, Whatman, NJ (USA). Analytical HPLC was also used to determine the specific radioactivity of the labeled compound. Biodistribution data were acquired by counting normal saline washed tissues after weighting on a CanberraTM high purity germanium (HPGe) detector (model GC1020-7500SL). Radionuclidic purity was checked with the same detector. For activity measurement of the samples a CRC Capintech Radiometer (NJ, USA) was used. All calculations and ITLC counting were based on the 511 keV peak. Animal studies were performed in accordance with the United Kingdom Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2nd edn.

$^{68}\text{Ge}/^{68}\text{Ga}$ Generator Quality Control

The simple prototype generator production has been already described in detail formerly, however few modifications were made to increase the efficacy of this generator [13]. Gamma spectroscopy of the final sample was carried out counting in an HPGe detector coupled to a CanberraTM multi-channel analyzer for 1000 seconds. Breakthrough was measured by counting the same sample 48 h after the first test for the detection of small amounts of Ge-68 in sample. Chemical purity control was carried out to ensure that the amounts of Sn, Zn, Fe, germanium and gallium ions resulting from the target material and backing in the final product are acceptable regarding internationally accepted limits.

Chemical purity was checked by ICP-OES method. The detection limit of our system was 0.1 ppm for all cations.

Preparation and Quality Control of ^{68}Ga -citrate

The production of the gallium-68 citrate has been already reported, however for the ease of high-scale production it was further modified and upgraded [14] slight modifications were made for this study. A nine-month old locally-available generator was used in the radiolabeling procedure. The acidic solution of [^{68}Ga]GaCl₃ with highest activity from the 3 first 0.5 mL-elution of the generator (1500 μL , 25 \pm 0.2mCi, in 0.6M HCl) was transferred to a 10 ml-borosilicate Reacti-vial containing solid HEPES (352 mg), acetate buffer 200 μl (0.1 M), and various Na citrate solution (20 mg/ml DDH₂O) and sealed vial was heated to 50-60 $^\circ\text{C}$ for 5-10 min. The mixture put in an ice bath for 2 min followed by the addition of 0.8 ml of normal saline. The reaction mixture was then injected into a 0.22 micron filter (Waters). The pH of the active solution with acceptable radiochemical purity was adjusted to 5.5. A 5 μl sample of the final fraction was spotted on a on Whatman No.2 paper and/or silicagel plates using Methanol/Ammonium acetate 10% (1:1), acetone/ glacial acetic acid (3:1) and normal saline as various mobile phases. HPLC was performed with a flow rate of 1 ml/min, pressure: 130 kgF/cm² for 20 min. HPLC was performed on the final preparation using a mixture of water:acetonitrile 3:2(v/v) as the eluent by means of reversed phase column Whatman Partisphere C₁₈ 4.6 \times 250 mm.

Biodistribution in Wild-Type Rats

The distribution of the radiolabelled complex as well as free Ga-68 cation among tissues was determined rats. The total amount of radioactivity injected into each rat was measured by counting the 1-ml syringe before and after injection in a dose calibrator with fixed geometry. The animals were sacrificed by CO₂ asphyxiation at selected times after injection (n=3 for each time interval), the tissues (blood, heart, lung, brain, intestine, faeces, skin, stomach, kidneys, liver, muscle and bone) were weighed and rinsed with normal saline and their specific activities were determined with a HPGe detector equipped with a sample holder device as percent of injected dose per gram of tissues.

Inflammatory Rat Models

The study was performed according to the guidelines and recommendations of the Committee on Animal Research at the Nuclear Science and Technology Research Institute. Ten female and male Sprague-Dawley rats (6–8 weeks old, 200–250 g weight) were provided by the Razi Institute, Karaj, Iran. They were housed five animals per cage under standard laboratory conditions at 25 $^\circ\text{C}$ and 50% humidity. They were allowed free access to food and water. Freshly autoclaved oil of turpentine (Cat No. 24245 Aldrich, 0.15 mL) was inoculated into the rats right thigh muscle to induce inflammation [15]. The mass of the inflammatory tissue grew to 10–15 mm during the experiments within 1–2 days after the turpentine oil inoculation. Their success criteria were difficulty in walking or lame behavior. Inflammation induction performed on a group of ten of rats. Seven rats with stable and successfully induced inflammation were used

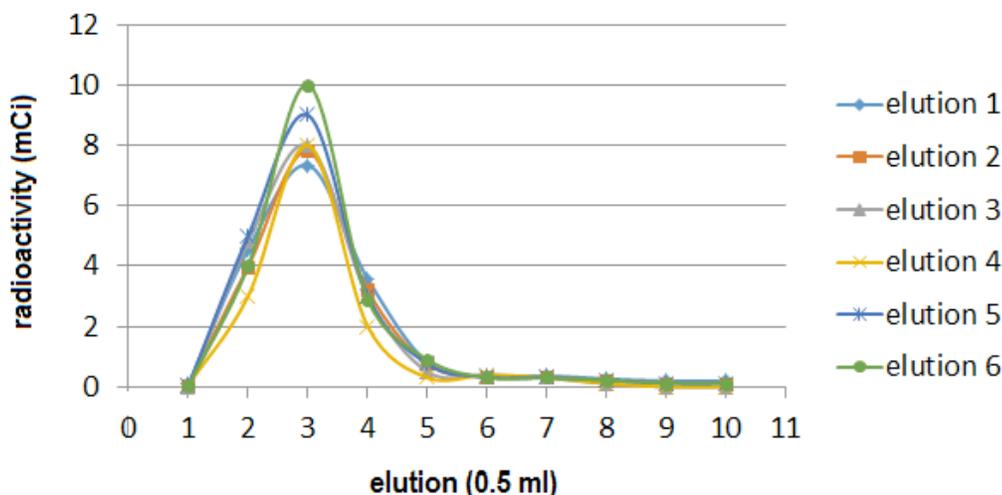


Fig. (2). Eluted 0.5-fractions from the Generator using 0.6 M HCl at optimized conditions at different working days.

for different time points (80, 140, 170, 200, 230, 260 and 290 min) after injection of the PET tracer above.

Imaging Studies

The imaging protocol was the same with already reported trend [16]. PET/CT imaging was performed with a PET/CT scanner (Biograph 6 TrueX; Siemens Medical Solutions). The rats were placed in a supine position. Static PET images were acquired for 10 min with 3 sets of emission images starting 80, 140, 170, 200, 230, 260 and 290 min after ^{68}Ga -citrate injection for the rats. In addition, PET emission scans were preceded by CT scans performed for anatomical reference and attenuation correction (spatial resolution 1.25mm, 80 kV, 150mAs) with a total CT scanning time of 20 s. Reconstruction was performed using the iterative algorithm with attenuation correction. The reconstruction settings were 4 iterations and 21 subsets to a 256×256 matrix, with a post filtering of 2 mm. Transmission data were reconstructed into a matrix of equal size by means of filtered back-projection, yielding a co-registered image set. The reconstructed emission images were reformatted into coronal, sagittal and maximum intensity projection (MIP) image sets.

RESULTS

Quality Control of ^{68}Ga Generator

Radionuclidic control showed the presence of 511 and 1077 keV all originating from ^{68}Ga and showed a radionuclidic purity higher than 99% (E.O.S.). For the quality control of the $^{68}\text{GaCl}_3$ solution, a time-activity study performed at the eluted sample after $\gg 10$ half-lives of the ^{68}Ga in order to check the ^{68}Ge breakthrough. The data was recorded up to 8 days after elution. Calculations showed that the $^{68}\text{Ge}/^{68}\text{Ga}$ activity ratio was 1.6600×10^{-5} at the time of elution. The concentrations of tin (from generator material), iron (from the sealing parts and acid impurities), zinc (as a decay product) and gallium (as the target material) were determined using inductively coupled plasma (ICP-OES) method all were less than 0.1 mg/L (limit of detection). The radio-

chemical purity of the $^{68}\text{GaCl}_3$ solution was checked in two solvents. In $10 \text{ mmol} \cdot \text{L}^{-1}$ DTPA aq. solution (solvent 1), free $^{68}\text{Ga}^{3+}$ is coordinated to more lipophilic moiety as $^{68}\text{Ga}(\text{DTPA})^{2-}$ and migrates to higher R_f . Small radioactive fraction remaining at the origin could be associated to colloids, since in presence of very strong complexing agent (i.e. DTPA), existence of other ionic species than $^{68}\text{Ga}(\text{DTPA})^{2-}$ is rare. On the other hand, using 10% ammonium acetate:methanol mixture (1:1) for the detection of other ionic forms of Ga-68 such as $^{68}\text{GaCl}_4^-$ showed radiochemical purity of higher than 99%.

The elution portfolio of the generator are important since the narrower the activity/volume peak, a sample with higher specific activity is obtained for radiolabeling however using 1M or higher concentration of HCl solutions although usually yield a better radioactivity peak/elution, however the formation of other gallium species not entering the radiolabeling occurred at these concentrations. By the choice of a suitable concentration (0.6-0.7M) most of daily generator eluted activity was obtained and also the peak of activity ranges for 0.5-1.5 ml of the first elutions (Fig. 2).

Radiolabeling

In the previous works the eluted activity was evaporated of followed by reconstitution in an appropriate buffer, however due to the limited physical half-life of the radionuclide, the addition of calculated amount of solid appropriate base/salt to the elution is proposed as a fast and reliable method. Using ITLC studies, the direct eluted sample from the generator using 0.6M HCl in normal saline migrates to higher R_f showing the possible existence of non-cationic form of Ga-68, using an appropriate buffering agent such as HEPES, the pH is adjusted to 4-5 and ITLC studies show a new peak demonstration Ga cation.

All considerations are taken into account for minimizing the reaction/purification/formulation process times. Evaporation of the eluent was replaced by the addition of the appropriate base (HEPES) as described above, heating the mixture would shorten the reaction time also should be carefully investigated. Citrate is a non-toxic ligand at milligram scales,

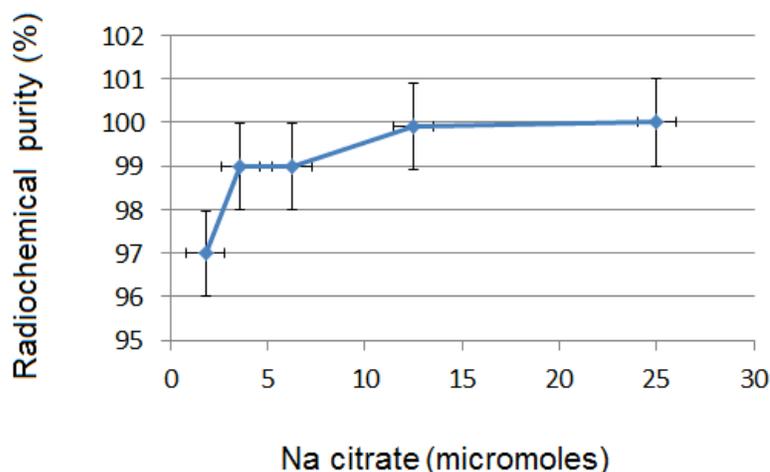


Fig (3). Amount of sodium citrate used for ^{68}Ga -citrate preparation at constant conditions (25 ± 1.23 mCi of Ga-68 activity, 352 mg of HEPES at 50-60°C for 5-10 min).

Table 1. Chromatographic properties of the systems used for ^{68}Ga -citrate radiochemical purity determination

Mobile phase	State phase	^{68}Ga -Citrate (R_f)	^{68}Ga -Chloride (R_f)
Methanol/Ammonium acetate 10% (1:1)	Whatman	0.45	0.70
Sodium acetate(1.5g)+ acetic acid (0.58 ml) in 100ml Water	Whatman	0.70	0.40
Acetone/ glacial acetic acid (3:1)	Whatman	0.10	0.45

leading to formulation problems if used in higher doses. A series of reactions performed in order to reach the minimal citrate amount needed leading to the application of 3.5-4 μM of sodium citrate used for a typical labeling reaching higher than 99% of radiochemical purity (Fig. 3).

Table 1 demonstrates the R_f s for various solvent mixtures and as well as stationary phases for radiolabeling reaction. The best system was considered acetone: glacial acetic acid (3:1) mixture in Whatman paper stationary phase.

HPLC studies demonstrated the existence of radiolabeled species using scintillation detector. A more fast-eluting compound at 3.17 min (scintillation detector) was observed for free gallium-68 cation while for ^{68}Ga -Citrate a second peak eluted at 4.93 min (scintillation detector). Both species are ionic and possibly using an ion chromatographic column would be of great value for characterization however, in our set-ups, the 5-6 min elution time, the two peaks are distinguishable using the mentioned system (data not shown).

Biodistribution

Biodistribution study was performed for ^{68}Ga -citrate and the %ID/g data are summarized in Figure 4. As reported previously, ^{68}Ga is excreted majorly from gastrointestinal tract (GIT) with high blood content due to transferrin binding at early time intervals (3.2% at 15 min), as well as significant lung, bone and stomach activity content is observed, kidney is not a significant accumulation site.

Liver is a major accumulation site for the transferrin and many radiolabeled proteins which with respect to ferric ion mimicking of Ga cation in body the liver could be a major site of accumulation in 60 min (17%). Lung and spleen are two important reticuloendothelial organs which macrophage

cells are located. The mechanism of Ga accumulation in WNCs and macrophage cells has been well documented [17] leading to high lung uptake (33% at 15 min). Significant cardiac uptake is also referred to ferric cation homology (10% at 15 and 120 min).

Imaging Studies

The early images as far as 80 min already showed the accumulation of ^{68}Ga in the site of inflammation while the trend continued up to 170 min after this time, the images did not show any distinct uptake. In 200 min post injection for instance there is no significant uptake difference among normal and inflamed animals.

DISCUSSION

Radiolabeling: Although the reaction would take place in presence of various citrate sources, using sodium citrate and presence of the HEPES as a buffering agent far better yields are obtained compared to the recent report [14]. On the other hand the reaction completed in an hour at room temperature, however applying gentle heat in a water bath at 50°C yields acceptable radiochemical yields. For the best performance, the generator must be eluted daily, even if not used on the date in order to remove the unwanted decay impurities or radiation induced impurities. Also when starting the production procedure the first fractions can be discarded. At a typical run the fraction 3-5 consist of the best specific activities daily available.

Animal model: Various animal models can be developed for inflammation studies. Nevertheless, animal models of rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis have been successfully used to enhance the un-

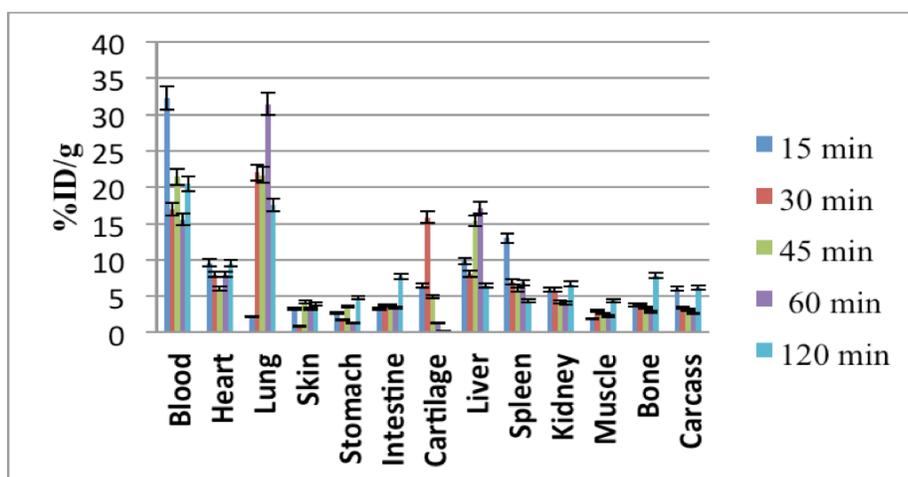


Fig. (4). Percentage of injected dose per gram (% ID/g) of ⁶⁸Ga-citrate in rat tissues at 15-120 min post-injection.

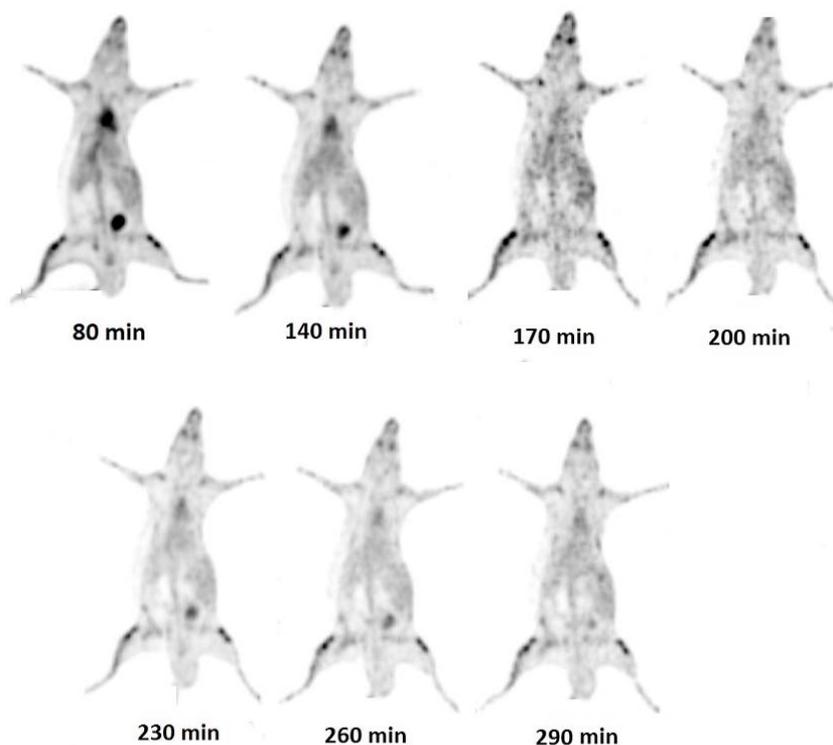


Fig. (5). PET MIP (Maximum Intensity Projection) images of ⁶⁸Ga-citrate 80-290 min after injection of 3.7 MBq in the inflamed rats.

Understanding of the human disease and have made significant contributions to the development of powerful new therapies [18].

There are newly developed animal models based on genomics tools with successful translation from mice to man while they are expensive to develop and not in access for many research groups and other models such as peritoneal cavity etc. have also been described [19]. The most accessible and understood animal model is the application of inflammation inducing agents such as caragenin and turpentine oils which the latter was used in this study.

Biodistribution: The biodistribution of free gallium cation has been reported in 72h time span using Ga-67 in

many reports [20]. ⁶⁷Ga is excreted majorly from gastrointestinal tract (GIT), thus colon, stool uptake are significant while blood stream activity is not majorly excreted from urinary system. For Ga-citrate however the data is accrued in shorter time span since the Ga as a homolog of ferric cation is bound to plasma proteins the blood content is high up to 2 h while the fate of transferrin and similar proteins is in the liver which is the final accumulation site as already can be seen in case of Ga-68.

Imaging: The best time of imaging is proposed 60-80 min after injection and image comparison at the 80 min time interval among a normal and inflamed rat obviously demonstrated the significant uptake in the inflammation foci (Fig. 6).

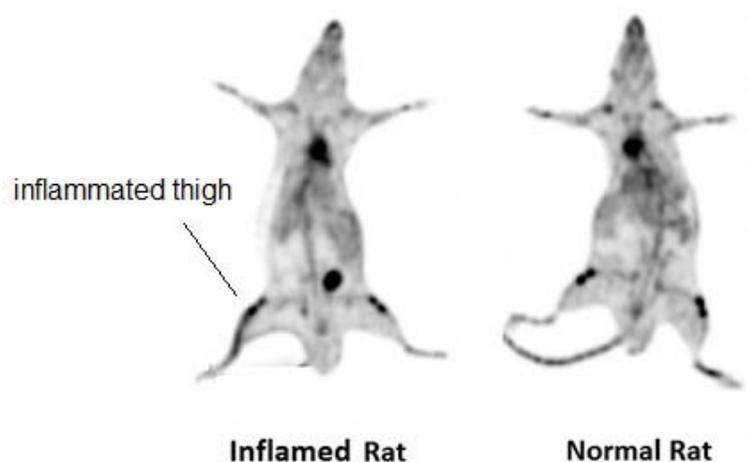


Fig. (6). PET MIP (Maximum Intensity Projection) images of ^{68}Ga -citrate 120 min after injection of 3.7 MBq in the normal and inflamed rat for better comparison.

The major difference between Ga-67 citrate imaging and Ga-68 imaging lies on the time span imaging possibility of each tracer, as understood, the gallium cation inflammation uptake is a fast accumulating event in the first few hours of the administration suiting the shorter half-life gallium-68 tracer while the other applications such as malignancy uptake studies occurring in 12-48 hours post administration requires a tracer with longer physical half-life, i.e. Ga-67 citrate.

CONCLUSION

In this study, ^{68}Ga -citrate was prepared with acceptable radiochemical purity (>99 ITLC, >98% HPLC), specific activity (28-30 GBq/mM), high chemical purity (Sn, Fe and Zn<0.1 ppm) in 15 min at 50°C. The biodistribution of ^{68}Ga -citrate was consistent with former reports up to 120 min. In PET/CT studies on inflamed rats it was shown that the best time of imaging is 60-80 min after injection. The image comparison at the 80 min time interval among a normal and inflamed rat obviously demonstrated the significant uptake in the inflammation foci. This study demonstrated small possible application ^{68}Ga -citrate using commercially available $^{68}\text{Ge}/^{68}\text{Ga}$ generator for PET imaging throughout the country.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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REFERENCES

- Firestone RB, Shirley VS, Baglin CM, Zipkin J. In: Table of isotopes. 8th edition, John Wiley and Sons, p.1447, New York, 1996.
- DDEP, Decay Data Evaluation Project Data, http://www.nucleide.org/DDEP_WG/DDEPdata.htm (2008).
- Burleson, R.L.; Johnson, M.C.; Head, H. Scintigraphic demonstration of experimental abscesses with intravenous ^{67}Ga citrate and ^{67}Ga labeled blood leukocytes. *Ann. Surg.*, **1973**, *178*(4), 446-52.
- Jalilian, A.R.; Novinrooz, A.; Motamedi-Sedeh, F.; Moradkhani, S.; Rajamand, A.A.; Solati, J. Evaluation of [^{67}Ga]Citrate in The Detection of Various Microorganism Infections in Animal Models. *Iran. J. Nucl. Med.* **2009**, *17*(2), 34-41.
- Nanni, C.; Errani, C.; Boriani, L.; Fantini, L.; Ambrosini, V.; Boschi, S.; Rubello D.; Pettinato, C.; Mercuri, M.; Gasbarrini, A.; Fanti, S. ^{68}Ga -citrate PET/CT for evaluating patients with infections of the bone: preliminary results. *J. Nucl. Med.* **2010**, *51*(12), 1932-6.
- Kumar, V.; Boddeti, D.K.; Evans, S.G.; Angelides, S. (^{68}Ga)Citrate-PET for diagnostic imaging of infection in rats and for intra-abdominal infection in a patient. *Curr. Radiopharm.* **2012**, *5*(1):71-5.
- Rizzello, A.; Di Pierro, D.; Lodi, F.; Trespidi, S.; Cicoria, G.; Pancaldi, D.; Nanni, C.; Marengo, M.; Marzola, M.C.; Al-Nahhas, A.; Rubello, D.; Boschi, S. Synthesis and quality control of ^{68}Ga citrate for routine clinical PET. *Nucl. Med. Commun.* **2009**, *30*(7), 42-5.
- Vorster, M.; Mokale, B.; Sathekge, M.M.; Ebenhan, T. A modified technique for efficient radiolabeling of ^{68}Ga -citrate from a SnO_2 -based $^{68}\text{Ge}/^{68}\text{Ga}$ generator for better infection imaging. *Hell. J. Nucl. Med.* **2013**, *16* (3), 193-8.
- Kumar, V.; Boddeti, D.K.; Evans, S.G.; Angelides S. ^{68}Ga -Citrate-PET for diagnostic imaging of infection in rats and for intra-abdominal infection in a patient. *Curr. Radiopharmaceut.* **2012**, *5*(1),71-5.
- Silvola, J.M.U.; I.; Sipilä, H.J.; Laine, V.J.O.; Leppänen, P.; Ylä-Herttua, S.; Knuuti, J.; Roivainen, A. Uptake of gallium-68 in atherosclerotic plaques in $\text{LDLR}^{-/-}\text{ApoB}100/100$ mice. *E.J.N.M.M.I. Res.* **2011**, *1*, 14.
- Hamazawa, Y.; Koyama, K.; Okamura, T.; Wada, Y.; Wakasa, T.; Okuma, T.; Watanabe, Y.; Inoue, Y. Comparison of dynamic FDG-microPET study in a rabbit turpentine-induced inflammatory model and in a rabbit VX2 tumor model. *Ann. Nucl. Med.* **2007**, *21*(1), 47-55.
- Jalilian, A.R.; Bineshmavasti, M.; Sardari, S. Application of radioisotopes in Inflammation. *Curr. Med. Chem.* **2006**, *13*, 959-965.
- Mirzaei, M.; Jalilian, A.R.; Badbarin, A. et al. Optimized production and quality control of ^{68}Ga -EDTMP for small clinical trials. *Ann. Nucl. Med.* **2015**, *29*(6), 506-11.
- Jalilian, A.R.; Aghanejad A.; Yousefnia, H.; Ardaneh, K.; Bolourinovin, F.; Bahrami-Samani A. Production and quality control of [^{68}Ga]Citrate for PET applications. *Asia Oceania J. Nucl. Med. Biol.* **2015**, *3*(2), 99-106.
- Jalilian, A.R.; Rowshanfarzad, P.; Shafaii, K.; Kamali-Dehghan, M.; Moafian, J.; Akhlaghi, M.; Babaii, M.; Rajabifar, S.; Mirzaei, M. Development of ^{111}In -DTPA-Human Polyclonal Antibody Complex for Long-term Inflammation/Infection Detection. *Nukleonika* **2005**, *50*(3), 91-96.
- Mirzaei, A.; Jalilian, A.R.; Shabani, G.; Mazidi, M.; Akhlaghi, M.; Beiki, D. Development of Ga-68 Ethyl Cysteinate Dimer for PET studies. *J. Radioanal. Nucl. Chem.* **2016**, *307*, 725-732.

- [17] Kamada, M. Distribution of ⁶⁷Ga-citrate in tumor tissues and various organs. *Radioisotopes (Tokyo)* **1978**, 27(7), 390-396.
- [18] Webb, D.R. Animal models of human disease: inflammation. *Biochem Pharmacol.* **2014**, 87(1), 121-30.
- [19] Blood-Siegfried, J. Animal models for assessment of infection and inflammation: contributions to elucidating the pathophysiology of sudden infant death syndrome. *Front. Immunol.* 2015, <http://dx.doi.org/10.3389/fimmu.2015.00137>
- [20] Jalilian, A.R.; Yousefnia, H.; Zolghadri, S.; Khoshdel, M.R.; Bolourinovin, F.; Rahiminejad, A. Development of radiogallium-ethylenecysteamine cysteine complex as a possible renal imaging agent. *J. Radioanal. Nucl. Chem.* **2010**, 284, 49-54.

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