ORIGINAL ARTICLE

The Evaluation of Contrast-to-Noise Ratio in CT Images Using Different Parameters of Gold Nanoparticles versus Omnipaque

Sara Khademi [1], Hosein Azimian [2], Hossein Ghadiri [3*]

[1] *Department of Radiology Technology, School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran*

[2] *Medical Physics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

[3] *Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

*Corresponding Author: Hossein Ghadiri
Email: h-ghadiri@sina.tums.ac.ir

Received: 08 November 2021 / Accepted: 12 December 2021

Abstract

Purpose: Gold Nanoparticles (GNPs) with high density and an atomic number have lately been proposed as an alternative contrast agent for Computed Tomography (CT).

Materials and Methods: In the present study, the Contrast-to-Noise Ratio (CNR) of GNPs from various shapes, sizes, concentrations, and surface chemistry was compared with an iodine contrast agent using CT at different X-ray tube voltages and concentrations.

Results: Our findings showed that GNPs in various concentrations, shapes, sizes, and X-ray tube energies from 80 to 140 kVp revealed greater image CNR than iodinated contrast media (Omnipaque). Smaller spherical GNPs (13 nm) had greater CNR than larger ones (60 nm) and Gold Nanorods (GNRs) with a larger Aspect Ratio (AR) represented excellent effect on CNR. In addition, Polyethylene Glycol (PEG) covering on GNRs decreased CNR. We observed image CNR was increased using increasing in kVp and concentration.

Conclusion: Smaller spherical GNPs can be proposed as a potential candidate as a future contrast agent alternative to iodinated contrast media.

Keywords: Gold Nanoparticles; Contrast-to-Noise Ratio; Iodinated Contrast Media; Computed Tomography.

DOI: https://doi.org/10.18502/fbt.v9i4.10420

1. Introduction

Computed Tomography (CT) is a medical imaging technique that is widely applied and has a great spatial resolution, and low cost [1]. Iodinated contrast agent with great X-ray attenuation has been applied for increasing CT image contrast. Furthermore, patient allergic reactions, renal toxicity, and short half-lives of iodinated agents provides short imaging times for technologist [2]. Platinum, bismuth, and gold nanoparticles (heavy elements) absorb X-rays more strongly than iodinated contrast agent [3]. The density and atomic number of iodine (4.9 g/cm^3 and z = 53, respectively) are lower than gold (19.32 g/cm^3 and z = 79) nanoparticles. The biocompatibility of Gold Nanoparticles (GNPs) with tissues compared to iodine contrast media provided its advantages to apply as a contrast agent in CT imaging [4, 5]. The biocompatibility of GNPs could be increased using Polyethylene Glycol (PEG) coating, therefore, it leads to provide enough time to collect GNPs in cells and produce higher contrast and improve the sensitivity of CT imaging [6, 7]. Many studies suggested GNPs as a contrast media for CT. For instance, Kim *et al.* [8] indicated that GNPs produce 1.9 times X-ray attenuation compared to Ultravist. Reported the GNPs produce contrast several times higher than iodine contrast agent. Jackson *et al.* [9] evaluated the effect of X-ray tube voltage on the Contrast-to-Noise Ratio (CNR) compared with iodine. Their results indicated that X-ray tube potential energy had a great effect on CNR of GNPs rather than iodine (from 1 to 2.1) when the tube potential was increased from 80 to 140 kVp. In this paper, spherical GNPs with different sizes (13 nm, and 60 nm), Gold Nanorods (GNRs) with different aspect ratios (Aspect Ratio (AR) = 2.4, and AR = 4.2), and GNRs with surface modified with PEG-GNRs were assessed to evaluate the CNR effect of the Nano Particles (NPs) and iodine as a contrast media in CT images. The size, shapes, concentration, and surface chemistry of GNPs were investigated as these have been considered as a principle factor to increase the contrast using different tube potentials. The CNR data effect of them was compared with iodine contrast agent (Omnipaque) at different tube voltages and concentrations.

2. Materials and Methods

2.1. Materials and Characterization

In the previous study, we synthesized and characterized GNPs with various sizes and morphologies [10]. In this fundamental study, the Transmission Electron Microscopy (TEM) was performed to assess the morphology, and size of the GNPs. The visible spectrum of GNPs was measured by using a SPEKOL 2000 spectrophotometer. In brief, the spherical GNPs (under reflux condition) were synthesized using the chemical reduction of Au+ ions with citrate ions. GNRs with different ARs (2.4, and 4.2) were synthesized via seed-mediated method. For reducing the toxicity of GNRs due to Cetyltrimethylammonium Bromide (CTAB), GNRs were centrifuged at 12,500 rpm for 11 mins twice. After that, 5 mL of mPEG-SH was added to GNRs with a larger AR and located in an incubator shaker for 24 h. The Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) was used to evaluate the concentrations of GNPs (at µg/ml). Raman Spectrometer (RS, Avantes) was used to evaluate the chemical component. NPs were diluted into Phosphate Buffer Saline (PBS) [10].

2.2. Imaging Protocols

GNPs with different sizes (13 and 60 nm), shapes (spherical and rod), and concentrations (200, 300, and 400 µg/ml) and iodinated contrast media (Omnipaque) at the equal concentration were prepared in 0.5 mL vilas and placed into Polymethylmetacrylic (PMMA) phantom. The samples were scanned by a CT imaging system (GE 64 slice) by the parameter of 80, 100, 120, and 140 kVp potentials. The slice thickness was set as 0.625 mm, 200 mAs, and pitch 1. Images were reconstructed by the standard method.

2.3. Image Analysis

After scanning, Images were transferred to a standard program (DICOM reader) and analyzed using drawing a circular Region of Interest (ROI) in three slices in each microtube (three samples in each concentration) and then the mean Hounsfield Unit (HU) data was evaluated. The noise was determined in the water as the Standard Deviation (SD) of the pixels. CNR data was measured from the recorded HU using plotting the ROI analysis across the image [11, 12]. In the following, the CNR formula was defined as (Equation 1):

$$CNR = \frac{(HU\ (sample) - HU\ (water))}{Noise} \qquad (1)$$

2.4. Statistical Analysis

All the data was evaluated for significant discrepancy in CNR using One-way analysis of variance and Tukey's multiple comparison tests. P-values less than 0.05 were performed as statistically significant.

3. Results

3.1. CNR of Various Sizes, Concentrations, and Shapes of GNPs versus Omnipaque in CT Imaging

Figure 1 indicates obtained CNR of GNPs and Omnipaque images a function of concentration. Both GNPs with different sizes, shapes, surface chemistry, and the iodine contrast media (Omnipaque) have revealed an increment trend of CNR by increasing concentration (Figure 1). At 300 µg/ml concentration and the same exposure factor (X-ray tube potential:140 kVp, scan slice thickness: 0.625 mm, 200 mAs, and pitch 1), the CNR value of the GNRs (AR = 4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG-GNR, GNPs (60 nm) was compared with Omnipaque and the CNR increased 5.1-times, 3.7-times, 2.53-times, 1.73-times, and 1.4-times, respectively. Overly, they were more effective than Omnipaque. At 200 µg/ml concentration and 140 kVp, the CNR value of the GNRs (AR = 4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG-GNR, GNPs (60 nm) was compared with Omnipaque and the CNR increased 4.33-times, 3.26-times, 2.3-times, 1.43-times, and 1.26-times, respectively. Overly, they were more effective than Omnipaque. The maximum CNR can be reached at 400 µg/ml for both GNPs and Omnipaque. The lowest CNR was formed at 200 µg/ml concentration for both GNPs and Omnipaque. Increased CNR for GNPs to Omnipaque was significant for 200, 300 and 400 µg/ml.

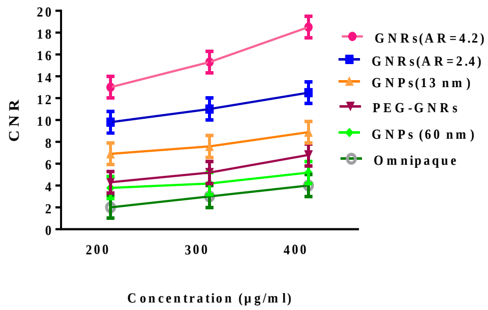

Figure 1. The CNR of different sizes, shapes, and surface effect of GNPs versus Omnipaque at different concentrations and 140 kVp tube potential

3.2. Effect of Different X-Ray Tube Voltages on CNR in CT Imaging

Figure 2 indicates CT images of GNPs with different sizes, shapes, surface chemistry, Omnipaque and water obtained under the same concentration (400 µg/ml) at different X-ray tube energies (80, 100, 120, 140 kVp). Figure 3 shows obtained CNR of images as a function of X-ray tube potentials (kVp). Each of NPs and Omnipaque have indicated an increase CNR value when imaged at superior X-ray tube potential. By increasing X-ray tube potential, CNR increases for GNRs (AR = 4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG-GNR, GNPs (60 nm),

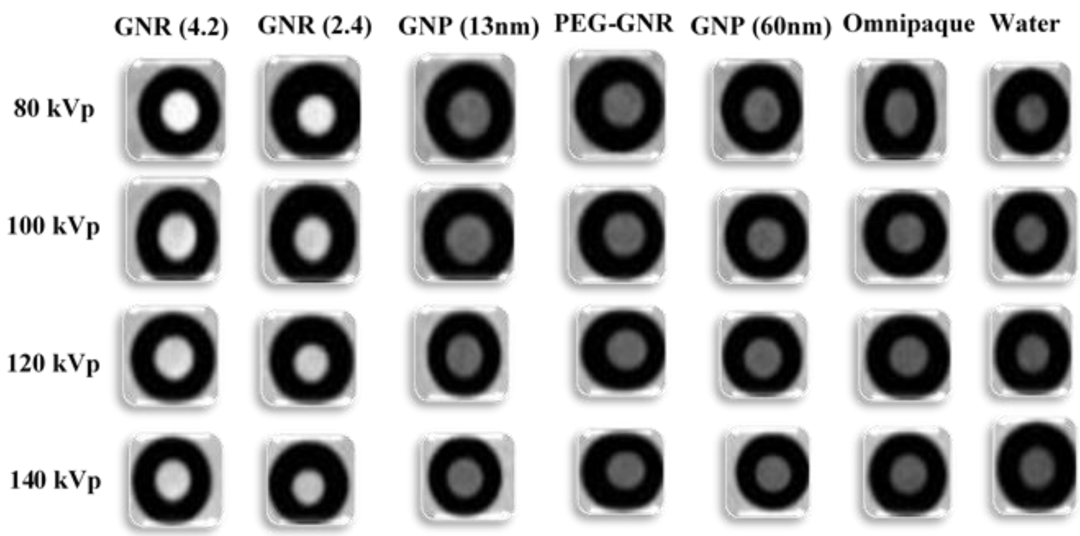

Figure 2. CT images of different sizes, shapes, and surface chemistry of GNPs, Omnipaque, and water at various X-ray tube at the concentration of 400 µg/ml

and Omnipaque, therefore, they have the maximum CNR value at 80 kVp (k-edge of iodine = 33.2 keV, k-edge of Au = 80.7 keV). GNPs with different sizes, shapes, and surface chemistry compared to Omnipaque increased CNR significantly for all X-ray energies (P-value < 0.05). At 400 µg/ml concentration and 80 kVp, the CNR value of the GNRs (AR = 4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG-GNR, GNPs (60 nm) was compared with Omnipaque and the CNR increased 4.30-times, 4.25-times, 1.73-times, 1.33-times, and 1-times, respectively. Overly, they were more effective than Omnipaque. At 400 µg/ml concentration and 100 kVp, the CNR value of the GNRs (AR = 4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG-GNR, GNPs (60 nm) was compared with Omnipaque and the CNR was increased 4.4-times, 2.68-times, 1.96-times, 1.43-times, and 1.26-times, respectively. Overly, they were more effective than Omnipaque. At 400 µg/ml concentration and 120 kVp, the CNR value of the GNRs (AR=4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG-GNR, GNPs (60 nm) was compared with Omnipaque and the CNR was increased 4.76-times, 3.3-times, 2.33-times, 1.66-times, and 1.4-times, respectively. Overly, they were more effective than Omnipaque. At 400 µg/ml concentration and 140 kVp, the CNR of the GNRs (AR = 4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG-GNR, GNPs (60 nm) was compared with Omnipaque and the CNR was increased 6.16-times, 4.16-times, 2.96-times, 2.26-times, and 1.73-times, respectively. Overly, they were more effective than Omnipaque.

Based on Figures 2 and 3, each of the concentration has indicated an increase of CNR data when imaged at higher X-ray tube potential (kVp). For the GNRs (AR = 4.2), GNRs (AR = 2.4), GNPs (13 nm), PEG- GNR, GNPs (60 nm), and Omnipaque, the CNR has reached up to 1.45, 1.61, 1.71, 1.7,1.73, and 1, respectively, higher than as CNR that achieved at 80 X-ray tube potential.

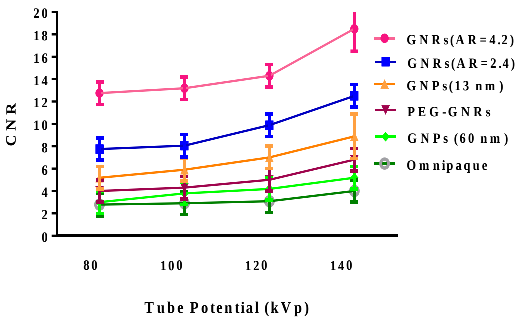

Figure 3. Obtained CNR of different sizes, shapes, and surface chemistry of GNPs and Omnipaque as a function of X-ray potential at the concentration of 400 µg/ml

4. Discussion

The CNR is defined as the capability of a scanning modality to show a specific structure versus to the surrounding area and its noise. In the present study, the CNR of spherical GNPs and GNRs at two various sizes and two various AR, respectively, and GNRs that coated with PEG was compared with Omnipaque at various concentrations and X-ray energies (kVp). GNPs with different sizes and shapes revealed higher image contrast enhancement than Omnipaque. The CNR value for Omnipaque and GNPs with different sizes and shapes increased using increasing X-ray tube potential (90, 100, 120, and 140 kVp) and concentrations (200, 300, and 400 µg/ml). The CNR data was maximum for GNPs at voltage 140 kVp in the same concentration with Omnipaque. At 140 kVp, the CNR value of GNRs with an Aspect Ratio of (AR=4.2), GNRs (AR=2.4), GNPs (13 nm) was approximately 6.16, 4.16, and 2.93-times, respectively, higher than Omnipaque. Both GNPs with different sizes and shapes and Omnipaque were indicated to elevate the highest CNR value at the maximum X-ray tube potentials (140 kVp). This is because the highest interactions of the X-ray photons have done after the threshold value of the k-edge. The k-edge of GNPs is at 80.7 keV, therefore the CNR value of GNPs is significantly more at X-ray tube voltage higher than 80 kVp. Increasing the X-ray tube energy led to reductions in the large of noise, therefore the CNR value increased. Jackson *et al.* [9] measured the CNR of gold nanoparticles versus iodinated contrast media at an equal concentration. Their results indicated that X-ray tube potential has a great impact on the CNR of the contrast agents. Their results showed, at the highest X-ray tube voltage, the CNR of GNPs was 114% higher than iodinated contrast agent. Galper *et al.* [13] revealed that CNR of GNPs is 1.9 times greater than iodinated contrast media at 120 kVp. In Kim *et al.*'s [14] comparison the CNR of GNPs is 1.9 times better than iodinated contrast media at the concentrations range of 1-3 M. In this study, the indicated GNRs with larger AR have the highest CNR than other NPs. A high concentration of CTAB is applied for the synthesis of GNRs. For reducing the toxicity of GNRs, it was centrifuged twice; however, more times in centrifugation can change the shape and morphology of NPs. Therefore, some CTAB could stay on the surface of NPs and even a small amount of CTAB is cytotoxic, thus GNRs are commonly found highly toxic even if GNRs are washed several times. Therefore, for reducing the cytotoxicity of GNRs, PEG molecules were replaced with the CTAB molecules on the surface of the particles [10]. After replacing PEG molecules with CTAB molecules, the CNR value was significantly reduced. As shown in Figure 3, though PEGylation was performed on GNRs (AR = 4.2), the PEG-GNRs revealed much smaller CNR value in contrast with both of GNRs (AR = 2.4 and AR = 4.2). Therefore, PEG covering on GNRs declined CNR. It can be the reason for the existence of CTAB in the form of two layers on the surface of GNRs, that it can simplify side-by-side arrangement of the GNRs, that results in their acting the same the larger structures with larger CNR value. It did not appear when GNRs were covered with PEG, therefore, a smaller CNR value was revealed [10]. On the other hand, smaller GNPs (13 nm) have a higher CNR value than a larger one (GNPs (60 nm)). Chenjie Xu *et al.* [15] indicated that the smaller size of GNPs increases the X-ray photon attenuation surface area that may cause more Signal-to-Noise Ratio (SNR) and better CNR. Zaky Harun *et al.* [16] indicated that the smaller size of GNPs (1.9 nm) has the highest CNR in all the X-ray tube potential. In sum, our findings showed that GNPs in all concentrations, shapes, sizes, and energies from 80 to 140 kVp reveal greater image CNR than iodinated contrast media (Omnipaque). It is significant to apply proper morphologies and sizes to improve CNR in CT. The proper GNPs for hospital diagnostic imaging must have compatibility in biology and adequately appropriate size for quality of imaging. For instance, GNPs with smaller sizes than 10 nm straight away eliminate from the body using the kidney and reduce the CNR value. As a consequence, smaller spherical GNPs could be proposed as a superior alternative to Omnipaque as a contrast media in CT. We observed image CNR was increased using increasing in kVp and concentration.

5. Conclusion

This fundamental research represented that the CNR could be suggested by the high atomic element of NPs. Therefore, better CNR could be provided by GNPs compared to Omnipaque. The CNR values of GNPs and iodinated contrast media increases using increasing X-ray potential (kVp) and concentration. At two different sizes, shapes, and surface chemistry of GNPs, in sum, smaller spherical GNPs (13 nm) can be proposed as greater instead of Omnipaque for CT. As future work, modifying GNPs with targeted ligands such as peptide and folic acid can elevate the contrast enhancement.

Acknowledgments

This research was supported by Tehran University of Medical Sciences, Tehran, Iran. (Grant (No: 30853)).

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