CT contrast agent of Platinum nanodendrites: Preliminary study

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Abstract. Platinum nanodendrites (PtNDs) are high-Z nanomaterials (Z=78) that possess a promising potential to be introduced as a novel contrast agent in diagnostic radiology. The objective of this study is to investigate the performance of PtNDs as contrast agent in computed tomography in term of CT number and CNR. PtNDs of different sizes (29, 36, 42, 52 nm) were prepared into final concentration of 1.0 mM in 3 mL syringes. CT scans were performed on PtND samples, distilled water and iodinated contrast agent arranged in phantom. The scans of each samples were conducted at 0.6 mm slice thickness and 80 kVp setting. CT number and contrast to noise ratio (CNR) were measured and calculated. The attenuation property of PtNDs shows size dependent characteristics, as the smallest PtNDs tested (29 nm) shows the lowest CT number (3.73±0.37), followed by 36 nm PtNDs (21.23±0.77), 42 nm (62.77±2.08) and 52 nm (89.33±4.60). CNR quantification reveals that there are no significant different of CNR values for PtNDs of size 29 nm, 36 nm, and 42 nm (around 24.67±0.25), while 52 nm PtNDs sees drop of CNR (20.14±0.57). Compared to iodinated contrast agent, 42 and 52 nm PtNDs show higher CT number, with slightly reduced CNR. This preliminary study suggests that PtNDs have the potential to be applied as contrast agents for CT imaging. The study also demonstrates that the performance of nanomaterial based contrast agent and x-ray attenuation properties are dependent on nanoparticles size and further study is required to elucidate multiparameter involved.

1. Introduction
Since its introduction in 1923, iodinated molecules have been widely applied as a contrast agent in x-ray imaging. After extensive research and development, current commercially available iodinated contrast media achieved significant improvements over their earlier versions, especially in term of their toxicity[1]. However, their administration still requires a high dose of iodine concentration, consequently pose several health hazards including renal toxicity, nephropathy and adverse cardiac events. They also possess nonspecific biodistribution and rapid renal clearance, hence retains short imaging window and often requires multiple injections per procedure [1, 2].

Novel high atomic number nanoparticles have been actively sought after as an alternative to the iodinated contrast agent, including gold nanoparticles [3], bismuth nanoparticles [4], and gadolinium nanoparticles[5]. Besides having higher atomic number and density compared to iodine molecules, their nano-dimension and unique pharmacokinetics also provide several advantages including enhanced...
blood residence time, and enabling either active- or passive-targeting toward a tumour or organ of interest[6].

Gold nanoparticles have received tremendous attention by the scientific community due to their favourable properties such as high x-ray attenuation coefficient, long vascular retention time and readily functionalized surface for enhanced colloidal stability and targeted delivery [1]. Sharing most of the gold nanoparticles unique characteristics, platinum nanoparticle is a potential candidate for application in the radiology department, especially as an x-ray contrast agent.

In this report, we assess the feasibility of a ‘naked’ platinum nanoparticles named Platinum Nanodendrites or PtNDs as an x-ray contrast agent. Our previous published report signifies the potential of PtNDs as a radiosensitizer in megavoltage radiotherapy [7]. Coupled with low cytotoxicity in their pristine form, PtNDs can be enhanced further in term of their size and surface functionalization to suit their diagnostic or therapeutic purposes. In this preliminary study, we limited the scope to only compare the PtNDs contrast enhancement against common contrast media used in x-ray radiology; iodinated contrast agent, to get a primary idea on PtNDs potential as their alternative. CT scan was used since this modality offers an excellent analysis of material’s attenuation properties.

2. Materials and Methods

2.1. Sample preparation
PtNDs were fabricated using a chemical reduction method [8]. The ratio of synthesis materials used in this study was similar to our previous report [7], to reproduce the PtNDs of size 29 nm, 36 nm, 42 nm and 52 nm. During the washing process, multiple batches of PtNDs were combined to achieve a high concentration of PtNDs in the stock solution. For this study, 3 mL of 1.0 mM PtNDs suspension was prepared and contained in syringes.

Commercial iodinated contrast agent used in this study was Iopamidol (Bracco Diagnostics Inc., USA). It was diluted to achieve similar volume and concentration with PtNDs and then contained in a 3 mL syringe. Other syringes also contained with a similar volume of air to act as the background, and distilled water to roughly simulate bodily tissue.

All syringes prepared were placed on the slots drilled on a polystyrene box as shown in Figure 1(a) in a circular manner around the centre hole. The centre hole drilled on the polystyrene box was aligned with the CT gantry isocenter so that all samples were located at equal distance from isocenter.

2.2. CT irradiation
Siemens SOMATOM Definition AS+ CT scanner (Siemens Healthcare, Germany) was used in this study as the imaging modality. The polystyrene box was strapped on CT table couch and positioned so that the centre of the box is aligned with the gantry isocenter (Figure 1(b)). The irradiation was performed with tube energy and effective tube current of 80 kV and 200 mAs respectively, while the slice thickness was set at 0.6 mm.
2.3. Data analysis
The images obtained were viewed and analysed on CT workstation preloaded with Syngo imaging software. A region of interest (ROI) with a dimension of 45 ± 1 mm² were delineated on each circular sample cross-sections. Mean CT numbers and the standard deviations for each sample were recorded based on multiple CT slices. Contrast-to-noise ratio, CNR was also calculated based on Equation 1 below [9]:

\[
\text{CNR} = \frac{\text{CT number}_{\text{samples}} - \text{CT number}_{\text{background}}}{\frac{1}{2} \left( \sigma_{\text{samples}} + \sigma_{\text{background}} \right)}
\]

where \(\sigma\) is the standard deviation. Comparison between PtNDs of different sizes versus iodinated contrast agent and distilled water were performed and discussed in the following section.

3. Result and Discussion
CT number is a parameter that can be easily obtained via a well-calibrated computed tomography scanner, and also the simplest way to define the attenuating property of certain materials. The formulation of CT number is directly related to linear x-ray attenuation coefficient of materials, \(\mu\), as shown in Equation 2 [2]:

\[
\text{CT number} = \left( \frac{\mu_{\text{material}} - \mu_{\text{water}}}{\mu_{\text{water}}} \right) \times 1000
\]

Theoretically, CT number of water is equal to 0, and other material’s CT number is ranged between -1000 up to 4000, depending on their x-ray attenuation coefficient relative to water. In this study, the CT number of PtNDs were compared with a commercial x-ray contrast agent; Iopamidol, at 1.0 mM concentration, and the result was plotted in Figure 2.
Figure 2. Comparison of CT number between PtNDs of different size and Iopamidol at 1 mM concentration.

The CT number of PtNDs of size 29 nm and 36 nm showed lower value compared to iodine (3.73 ± 0.37 and 21.23 ± 0.77 respectively), while 42 nm and 52 nm PtNDs possessed higher value (62.77 ± 2.08 and 89.33 ± 4.60 respectively). This result signifies that particle dimension played a huge role in manipulating the attenuation property of PtNDs. This result conforms to other literature where the attenuation property of nanoparticles is proportional to their size. For example, a study by Liu et al., 2010 on dendrimer-stabilized silver nanoparticles, Ag DSNPs, shows that larger nanoparticles possess higher CT number [10]. They suggested that this phenomenon was due to a higher concentration of Ag with the size of Ag DSNPs. When compared with an iodinated contrast agent (Omnipaque) at the same concentration, the CT number of Ag DSNPs are almost the same with iodine, despite Ag possess lower atomic number than I. Their data proved that the colloidal property of Ag DSNPs plays a huge role in enhancing their attenuation property.

However, the contradictory result was provided by Xu et al., 2008, where gold nanoparticles (GNPs) of smaller size possess greater CT number than GNPs of larger sizes [11]. With the same concentration, smaller GNPs offer larger cumulative surface area. The possibility of interactions between radiation and materials are dependent on the surface area of the materials, therefore smaller GNPs has higher chance in attenuating radiation compared to larger GNPs, hence produced higher CT number.

CT number formulation is based on linear attenuation coefficient, $\mu$, of tested materials. Therefore it is of highly important to discuss the parameters within the coefficient itself as the main contributing factor to the materials attenuation property. The equation for the coefficient is denoted as follows (Equation 3):

$$\mu = \frac{\rho Z^4}{AE^3}$$  \hspace{1cm} (3)
where $\mu$ is directly proportional to material density ($\rho$) and atomic number ($Z^4$), while inversely proportional to atomic mass ($A$) and x-ray energy ($E^3$) [2]. The relation between the attenuation properties of PtNDs across different size can be associated with the increment of Pt density within the sample. PtNDs with smaller size might possess a higher surface area and dispersed well within the medium, but the nanoparticles core’s density is lower, causing a detrimental effect on their x-ray attenuation capability. Based on our result, we suggest that PtNDs need to be large enough (>40 nm) to provide contrast enhancement on par or superior to the iodinated contrast agent.

![CNR analysis of PtNDs of difference sizes and iodinated contrast agent.](image)

**Figure 3.** CNR analysis of PtNDs of difference sizes and iodinated contrast agent.

Opposing to CT number data, contrast-to-noise ratio analysis of PtNDs and Iopamiro as shown in Figure 3 demonstrated that all PtNDs possess lower CNR value as compared to Iopamiro. The CNR for PtNDs of size 29 nm, 36 nm, 42 nm and 52 nm are 25.03 ± 1.11, 24.47 ± 1.22, 24.52 ± 0.46 and 20.14 ± 0.14 respectively. In other words, PtNDs provided noisier images compared to iodine (CNR=37.14). Our result contradicted with the result provided by Jackson, Rahman [3], where they demonstrated that gold nanoparticles, AuNPs with the average size of 1.9 nm are capable of enhancing CNR by 14% at the same x-ray tube energy (80 kV).

The inferior CNR value of PtNDs against Iopamiro can be correlated with the dispersion of contrast materials within the medium. Iodinated contrast agent consists of small molecules that are homogeneously dispersed within the sample solution, providing images with low noise, and in turn, high CNR value. PtNDs on the other hand, consist of discrete particles dispersed within the medium. The image noise becomes more prominent at higher PtNDs size as shown in Figure 3, where there is a drop of CNR value for 52 nm PtNDs compared to other PtND sizes. Interestingly, AuNPs used in previous literature also possess significantly small dimension compared to PtNDs used in this study (1.9 nm), which may perhaps contribute to the dispersion homogeneity within the medium.

As discussed earlier, PtNDs of larger size possess a higher density of Pt elements within their core. While the attenuation property was heightened, their dispersion within the medium is diminished, causing higher noise in the image. It should be noted that at higher concentration, PtNDs dispersion within the medium should be enhanced, hence reduces the image noise substantially. However, based
on our previous study [7], there is a slight correlation between PtNDs concentration and their cytotoxicity. Therefore it is important to fabricate the PtNDs of accurate size range and concentration to strike a balance between their contrast enhancement with the image noise while maintaining favourable toxicology profile for clinical use.

4. Conclusion
We demonstrated that PtNDs possessed promising potential to be used as x-ray contrast agent. The attenuation of PtNDs is highly proportional to their particle dimension. However, larger PtNDs contribute to higher image noise, therefore it is important to strike a balance between contrast enhancement and image noise when designing PtNDs for the x-ray imaging application.

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