EC CLINICAL AND EXPERIMENTAL ANATOMY
Research Article

A Comparison Study on Contrast Agents between Lead Oxide and Iopamidol Using for Three-dimensional Reconstruction of Blood Vessels in Isolated Placenta

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Received: March 16, 2020; **Published:** April 13, 2020

Abstract

Background: The aim of this study was to investigate the image for three-dimensional reconstruction of blood vessels in isolated placentas after using lead oxide or iopamidol as contrast agent.

Methods: A prospective study was conducted within 20 normal human placentas donated from puerperal without complications during pregnancy in the Second Hospital of Anhui Medical University from December 2015 to February 2016. The placentas were divided into two groups and each group had 10 samples. Lead oxide or iopamidol was injected into both umbilical arteries and veins separately. Then CT scan was performed and post processing the images of placental blood vessels was completed using three-dimensional reconstruction technique. Placental volume, vascular volume and vessel diameters of different branches were measured. Data were analyzed between groups using Student's t-test.

Results: The images of the primary and secondary vascular branches of the placentas using lead oxide as contrast agent were in the strong three-dimensional sense without obvious artifacts, while the tertiary and fourth branches in the images looked blurred, and the microvascular of the placental lobular in the images looked sparse. On the contrary, the primary and secondary branches in the images using iopamidol as contrast agent were not so strong three-dimensional sense, while the tertiary and fourth vascular branches' perfusion had less peripheral vascular artifacts compared with the lead oxide group. The value of placental volume and vascular volume between the lead oxide and iopamidol groups had no significant difference ($P > 0.05$). The value of the diameter in the primary and secondary branches in the lead oxide group were significantly greater than that in the iopamidol group, while the value of the diameter in the tertiary and fourth branches were obvious smaller than that in the iopamidol group ($P < 0.05$).

Conclusion: Lead oxide is more suitable for displaying the three-dimensional reconstruction images in primary and secondary vascular branches of the placentas, while iopamidol is more suitable for displaying the three-dimensional reconstruction images in the third and fourth branches. Quantitative measurement of the three-dimensional reconstruction blood vessels may be used as a basic measurement during placental vascular research.

Keywords: *Lead Oxide; Iopamidol; Placenta; Three-Dimensional Reconstruction; Contrast Agent*

Introduction

Material and nutrient exchanges between mother and fetus mainly completed through placental blood vessels [1]. Current research on placental blood vessels has gradually attracted the attention of obstetricians. Early research on placental vascular morphology focused on vascular casts. Disadvantages of vascular casting specimen research included long time preparation, easily broken, and not easy to be stored and measured like the length and diameter of the vascular casts. Therefore, vascular casting technology cannot be used to fully understand the placental blood vessels [2]. With the development of CTA (computer tomography angiography) technology in recent years, it is possible to display the 3D structure of human body and measure the diameter, length and angle of vessel branches accurately using CTA technology. Nowadays, CTA technology is mainly used at the study of coronary artery disease, cerebrovascular disease and the diagnosis of malignant tumors [3-6]. Instead, there are few reports in the literature using CTA to study placental vascular structure. This study intends to explore the general rules of normal placenta vessels distribution using CTA technology by comparing the 3D images of placental blood vessels using lead oxide or iopamidol as contrast agent.

Materials and Methods

Research materials

From December 2015 to February 2016, twenty isolated placentas were collected after vaginal delivery in the Obstetrics Department of the Second Hospital of Anhui Medical University. Inclusion criteria: (1) the gestational week of delivery was 37 - 42 weeks; (2) no complications occurred during pregnancy and delivery; (3) all isolated placentas were intact; (4) all the placental lobules, membranes and umbilical cord were not damaged. Exclusion criteria: (1) premature or overdue delivery; (2) had complications history during pregnancy, such as gestational diabetes, hypertensive disorders of pregnancy, etc. (3) Vascular rupture of umbilical cord roots, placental lobules and membrane after delivery. This study was approved by the Ethics Committee of the Second Hospital of Anhui Medical University (No. LLSC20150209). All women in the study signed the consent to donate the placenta to the hospital.

Reagents

Self-setting dental tray water, self-setting dental tray powder (Shanghai New Century Dental Materials Co., Ltd.), dibutyl phthalate (Wuxi Prospect Chemical Reagent Co., Ltd.), iopamidol (Shanghai Boleco Xinyi Pharmaceutical Co., Ltd.), lead oxide powder (Shanghai Aibi Chemical Co., Ltd.).

Placental vascular perfusion

After delivery, the placenta was collected and careful examined to excluding vascular injuries. Umbilical cord of the placenta was kept as long as 6cm for vascular perfusion. The umbilical arteries and veins were separated by vascular forcep and marked with suture silk [7]. No. 18 and No. 20 rat's gastric needles were inserted into the umbilical arteries and veins respectively, fixed with suture silk in order. Preheated heparin sodium physiological salt (100U of heparin sodium added into 500 mL of normal saline and kept the temperature at 37 degrees) infused into the placental blood vessels through the rat's gastric needles until the rinsing liquid was clear without visible pink color (Figure 1). A simple randomized grouping method was used to divide the placentas into iopanol group and lead oxide group, with 10 cases in each group.

Figure 1: *After the placenta are pretreated, the fetal side of the placenta can see the blood vessels in the placenta which are full and the color is transparent.*

Configuration of perfusion solution: 15 ml of self-setting dental tray water and 5 ml of dibutyl phthalate, added an appropriate amount of red or blue pigment, stirred for 2 - 3 minutes. Then, ten gram self-coagulated dental tray powder with 5 mL iopanol (containing 370 g/L of iodine) or 1.6g lead oxide powder were added and stirred for 2 - 3 minutes. 50 mL iodine solution containing red iodoparol or lead oxide, and 50 mL iodine solution containing blue iodoparol or lead oxide were prepared for umbilical artery and vein perfusion [8].

Red iodopalm or lead oxide solution were injected into the placental arteries of each group at 10 ml per minute using a 50 ml syringe. Injection procedure would be stopped once the placenta vessels at the fetal surface were full of iodine solution. After that, we removed the gastric needles and ligated the umbilical arteries. According to the same procedure mentioned above, the blue iodoparol or lead oxide solution were injected into the placental vein of each group (Figure 2). The enhanced CT scan was completed 30 minutes after the injection procedure.

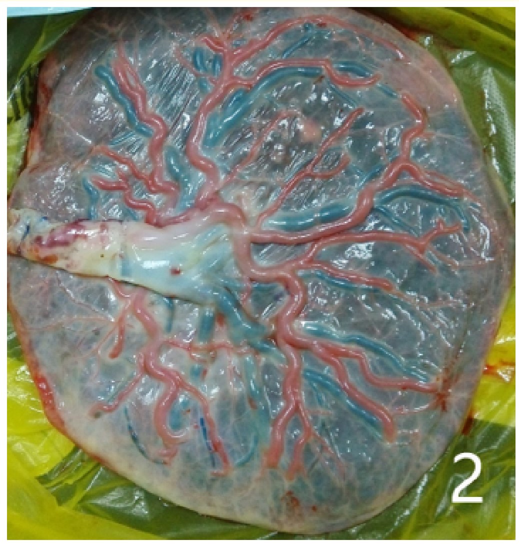

Figure 2: *The fetal surface of the placenta shows red arteries and blue veins filled with umbilical arteries and venous filling after vascular perfusion.*

3D model measurement of placental blood vessels

GE 64 row Light speed VCT (American General Corporation) was used to perform conventional axial plain scan on placental specimens that had completed vascular perfusion. Placenta was laid flat with fetus facing up and maternal facing down. CT scanning parameters: tube voltage 120 kV, tube current 280 mA, scanning layer thickness 0.625 mm, layer spacing 0.625 mm. 3D images of the placental arteriovenous vascular network was automatically generated using VR method on the GE Adw 4.4 workstation after the scan.

The placental vascular volume and vessel diameter of the two groups were measured respectively using GE Adw 4.4 workstation software package. The umbilical veins were traced in sequence from the primary vascular branches to the fourth vascular branches and the vascular diameter in each branches were measured. Because the vessels from the fifth to seventh vascular branches in the two groups were poorly displayed, this study only analyzed the characteristics of the blood vessels from the primary branches to the fourth branches.

Statistical methods

Data were analyzed using SPSS17.0 software. The Student's t-test was used to compare the vessel diameter and vessel volume parameters of the placentas between the iopanol group and lead oxide group. In all statistical analyses, $P < 0.05$ was considered statistically significant.

Results

During the experiment, contrast extravasation in a placental specimen in the iopamidol group affected the measurement of placental volume and diameter of the umbilical vein in 3D images, while an unsuccessful contrast infusion in a placental specimen happened in lead oxide group. This study successfully completed contrast medium perfusion and 3D imaging reconstruction in 18 placental specimens.

No significant difference could be found in placental blood vessel volume between the lead oxide group and iopanol group ($P > 0.05$) (Table 1). The diameters of the primary and the secondary vessel branches of the placentas in the lead oxide group were larger than those in the iopanol group, while the diameters of the tertiary and fourth vessel branches of the placentas were smaller than those in the iopanol group, (all $P < 0.05$) (Table 2).

Groups	Number of Cases	Placental Volume	Vascular Volume
Lead oxide group	9	626.14 ± 164.76	195.11 ± 64.91
Iopanol group	9	611.83 ± 93.00	194.11 ± 104.87
t		0.227	0.024
P		> 0.05	> 0.05

Table 1: *Comparison of placental volume and placental vascular volume in lead oxide group and iopanol group ($\bar{x} \pm s$, cm^3).*

Groups	Number of cases	Primary vascular branches	Secondary vascular branches	Tertiary vascular branches	Fourth vascular branches
Lead oxide group	9	11.34 ± 2.06	9.76 ± 0.98	4.44 ± 0.52	3.49 ± 0.42
Iopanol group	9	9.38 ± 1.22	7.65 ± 0.54	6.16 ± 0.74	5.06 ± 0.69
t		2.469	8.015	-8.029	-8.236
P		< 0.05	< 0.05	< 0.05	< 0.05

Table 2: *Comparison of measured diameters of umbilical veins at different levels of placenta in lead oxide group and iopanol group (mm, $\bar{x} \pm s$).*

The primary and the secondary vascular branches of the placentas in the lead oxide group, had good vascular perfusion, strong stereoscopic sense and without obvious artifacts around the blood vessels compared with the iopanol group (Figure 3). However, the tertiary and fourth vascular branches of the placentas in the lead oxide group do not had very good vascular perfusion and strong stereoscopic sense compared to the iopanol group due to the large molecular weight as the contrast agent for lead oxide solution (Figure 4).

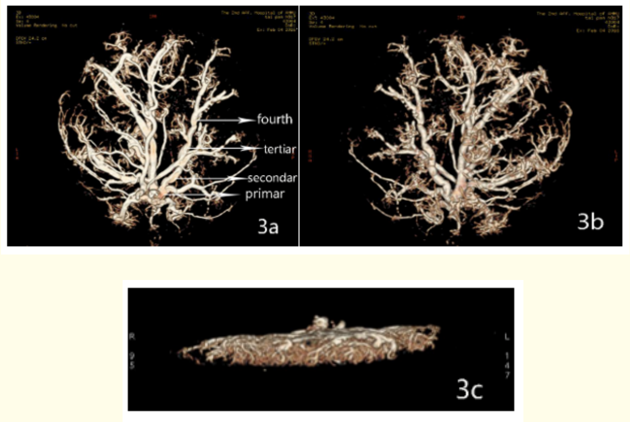

Figure 3: *3D reconstruction of placental umbilical vein CT angiography in the lead oxide group.*
3a: Placenta fetal surface: the primary to secondary vascular branches of placenta were thick and clear in development; the tertiary and fourth vascular branches were sparse and unevenly distributed.
3b: Placenta maternal surface: microvasculature and placental lobules were rare.
3c: Side of the placenta: the placenta was uneven in thickness, and there were many sparse holes below.

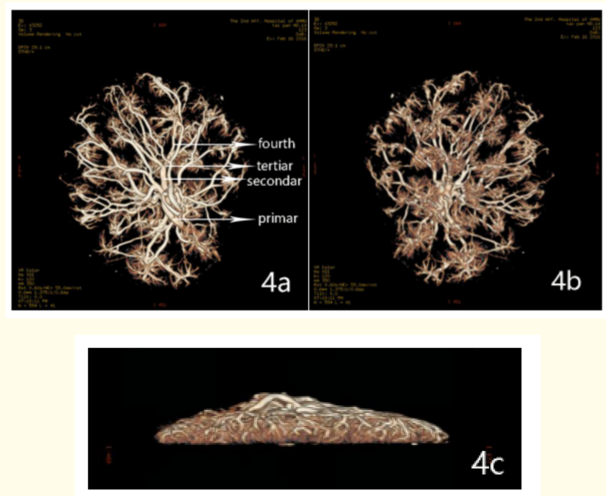

Figure 4: *3D reconstruction of placental umbilical vein CT angiography in the iopanol group.*
4a: Placenta fetal surface: the primary to secondary vascular branches of placenta were slender, and the development was not clear in the lead oxide group; the tertiary and fourth vascular branches were abundant and evenly distributed.
4b: Placenta maternal surface: microvasculature and placental lobules were rich and full.
4c: Side of the placenta: the placenta had a uniform thickness, and there were no holes in the branch vessels.

Discussion

In the past few years, vascular casting technology was the main method for vascular morphology research. Gong., *et al.* [9] observed and analyzed the characteristics of different vascular cast in normal and pathological placentas. He found vascular cast had many disadvantages such as high brittleness of the blood vessels, easy damage to the model, fading and difficult to save, which limited its application range. With the development of digital medicine, the advent of 3D reconstruction technology of placental blood vessels had made up for the shortage of vascular molds. It could not only be stored permanently and has good stereoscopic effect, but also could measure the fourth to seventh vascular branches of the placentas. At present, in the 3D reconstruction of placental blood vessels, the more commonly used angiographic agents are lead oxide and iopanol, while the contrast effect and application scope of the two are not clear. Therefore, the purpose of this experiment is to compare and analyze the development effect of lead oxide and iopamidol in 3D reconstruction of isolated placental blood vessels.

Lead oxide was originally used in vascular molds because of its large molecular weight and insolubility in water. Later, it was used as an important part of angiography because it was not easy to leak out of blood vessels. Hao., *et al.* [10] showed that the advantages of lead oxide contrast agents were strong light-shielding properties, which could make blood vessels images clearly, and did not agglutinate when formulated. Lead oxide solution should not be left too long after shaking, preferred perfusing within 3 minutes. Wang., *et al.* [2] studied the modified dental tray powder plus lead oxide powder as a contrast agent which could clearly show the blood vessel running and branching conditions in angiography. Studies had shown that sufficient amount of contrast agent must be added when the filler was formulated (100 mL of the filler contains 8g of lead oxide powder). Stirred thoroughly before used so that the contrast agent was evenly mixed in the filler as much as possible during the reconstruction process. The purpose was to reduce the distortion incompleteness, or discontinuity of the reconstructed blood vessel caused by uneven filling of the agent [2]. In this study, we found that the diameter of the primary and the secondary branches of the placentas in the lead oxide group were larger than those in the iopamidol group, while those the tertiary and fourth branches of the placentas were smaller than those in the iopanol group. The reason maybe due to that lead oxide powder was powdery. After mixing with the filler, the viscosity of the filler was increased, which causes the resistance of the filler to enter the microvessels increased under the same perfusion pressure, and the microvessels could not be imaged.

Iopamidol injection was a non-ionic water-soluble iodine contrast agent, which had a good development effect, low toxicity to blood vessel walls and nerve tissues, less adverse reactions, stable properties, and a wide range of applications. It was mainly used for neuro-radiology, angiography, Urinary system angiography, enhanced scan in CT examination, arthrography, fistula angiography, DSA, etc [11]. Li., *et al.* [12] found that 3D images of placental vascular tree could be obtained by CT angiography and 3D reconstruction of isolated placenta through umbilical artery and umbilical vein perfusion with different concentrations of iodine contrast agent. The arteries could show fifth to sixth vascular branches, and the veins could show fourth to fifth vascular branches. Clinically-used iodine contrast agents such as iopamidol could be completely applied to 3D reconstruction of placental blood vessels. In this study, one of the ten placentas in the iopamidol group failed 3D reconstruction. The reason was that the CT scan was not performed in time after the placenta was filled with the filler. And the iodoparol in the blood vessels leaked out of the placental tissue. Density and placental tissue density were uniform and could not be reconstructed in 3D. Therefore, CT scan should be performed within 30 minutes after the end of perfusion when using iopanol. In this study, the molecular weight of iopamidol was lighter compared to lead oxide, so the placental umbilical veins development in the iopamidol group were not as good as those in the lead oxide group. However, the iopamidol contrast agent was a high-density solution and mixed in the filler. After diluting the filler, under the same perfusion pressure, the resistance of the filler enter the microvasculature was smaller. Therefore, the contrast of iopamidol in the microvessels and placenta lobes was full, and the blood vessel shape was natural.

In this study, due to the elasticity of the blood vessels in the placental vein, when the vein was perfused alone, the blood vessels would be distorted and lose their original shape. Therefore, the author choosed to perfuse arterial blood vessels first, and then perfuse venous blood vessels to ensure the original direction of venous blood vessels on the greatest extent.

Conclusion

In this study, the contrast effect of lead oxide and iopanol in 3D reconstruction of placental blood vessels was compared for the first time and the placental volume, blood vessel volume, and diameters of different vascular branches of the umbilical vein were measured. The results showed that lead oxide contrast agent had the advantages of full development, strong three-dimensional sense and no obvious artifacts around the blood vessels for the primary and the secondary branches of the placentas with a diameter from 8.82 mm to 13.36 mm. The iopanol contrast agent had the advantages of clear development, natural blood vessel flow, microvessels and placenta lobes uniform development for placenta umbilical vein the tertiary and fourth vessel branches with a diameter from 4.41 mm to 6.94 mm. Therefore, the author believe that for the selection of contrast agents in the study of placental blood vessels, the diameter of the blood vessel branches measured according to specific experimental requirements should be selected. If it is necessary to see the main blood vessels, it is recommended to choose lead oxide contrast agent. If branches of blood vessels in some diameter need to be clearer, it is recommended to choose iopanol contrast agent.

There are still some limitations in this study. The sample size of the study is small. No length measurement of each vessel branches had been done due to the distortion of the vessels at various levels. It is necessary to expand the sample size and find better methods to collect more data which include vessel length and vessel angle measurements in the follow-up studies.

Funding

National Natural Science Foundation for Young Scholars (No. 81100412); Outstanding Young University Talents Project of Anhui Province (No. gxyqZD2016060); China Postdoctoral Science Foundation (No. 2016M592038); Anhui province public welfare research project (No. 5101ID04041).

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Volume 3 Issue 5 May 2020