

The possibility of using radiopaque and magnetic resonance agents to reduce light scattering by human nail bed tissues

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In the paper the possibility of using radiopaque and magnetic resonance agents, which are already used in clinical practice, for optical clearing of biological tissues was investigated. In vivo measurements of the degree of tissue optical clearing and evaluation of the effectiveness of the studied agents were carried out in the area of the nail bed of a human finger using optical coherence tomography technique. It was shown that almost all the agents used are effective for optical clearing of the tissue in the studied area at certain depths. For example, after applying the gadovist[®] magnetic resonance agent, the extinction coefficient of probing beam decreased by $16 \pm 8\%$ at a depth from 0 to $50\mu\text{m}$. When using visipacue[®] radiopaque agent in combination with polypropylene glycol, the extinction coefficient decreased by $30 \pm 13\%$ for the same depth. The results of the work make it possible to expand application scope of radiopaque and magnetic resonance agents to optical clearing of tissues and visualization of capillaries.

Keywords: Optical clearing, radiopaque agents, magnetic resonance agents, optical coherence tomography, extinction coefficient.

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1. Introduction

Optical methods for studying biological tissues and organs have become widespread over the past 20 years. High light scattering and absorption of light by biological tissues is the main factor limiting their use [1,2]. Various methods, in particular optical clearing are used to overcome these limitations and increase both the contrast of noninvasive imaging of subcutaneous structures (for example, capillaries) and the depth of penetration of visible and near-infrared radiation into biological tissues [3]. The substances used for this purpose (glycerin, glucose, etc.) are called optical clearing agents (OBA). The mechanism of optical clearing is based on the diffuse penetration of OBA into the deep layers of tissues, resulting in a decrease in the contrast of the relative refractive index between light-scattering optical inhomogeneities in the surrounding tissue. This leads to a reduction in the multiple scattering of light, which makes the tissues optically more homogeneous and transparent [4]. As a result, the depth of penetration of light (probing radiation) increases and the resolution of imaging methods increases, for example, digital capillaroscopy for imaging terminal capillaries in the human nailbed *in vivo* [5]. In addition, applying OBA to the surface of the tissue (skin) can reduce its reflection coefficient, which also helps to visualize deeper layers of the object under study. Currently, magnetic resonance (MR) agents are widely used in clinical practice to increase the contrast of MRI images obtained as a result

of patient diagnosis. These agents, for example magnevist[®] and gadovist[®], are administered intravenously [6]. Radiopaque (RO) agents are used to improve the contrast of X-ray images, for example, the visipacue[®], omnipaque[®] and accupacue[®] used in this study. The principle of operation of these substances is based on the fact that the iodine atoms in their composition absorb X-ray radiation more strongly [7]. As a result, the contrast between the agent-containing and non-agent-containing tissue increases. These preparations can potentially be used not only for MRI and X-ray diagnostics, but also to improve optical imaging of tissues due to reduced light scattering.

The purpose of this paper was to study the possibility of using MR and RO agents, which are already used in clinical practice, to improve the visualization of subsurface structures of human finger tissue *in vivo*. Measurements were carried out in the area of the nailbed using optical coherence tomography (OCT).

Materials and methods

Six different substances and their mixtures were used in the work, including magnevist[®] (dimeglumine gadopentate, mol. weight 938.02 g/mol, 0.5 mmol/ml, Bayer HealthCare Pharmaceuticals, Germany), gadovist (gadobutrol, mol. weight 604.72 g/mol, 1.0 mmol/ml, Bayer HealthCare Pharmaceuticals, Germany), visipacue blend[®] (iodixanol

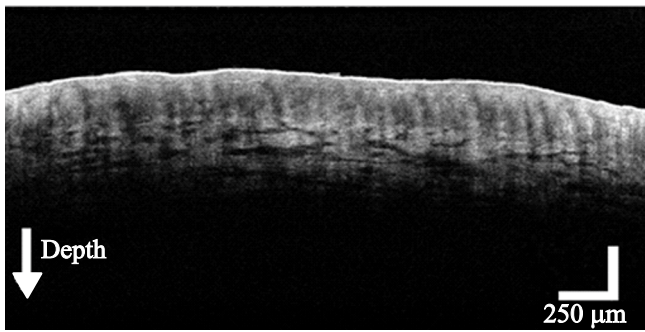


Figure 1. A typical two-dimensional image of the skin area of the human nailbed in a depth section, obtained using OCT.

1550 g/mol, GE HEALTHCARE, AS, Norway) 90 % and dimethyl sulfoxide 10 % (DMSO), a mixture of visipacue® 40 % and polypropylene glycol 400 60 %, accupacue® (yogexol, mol. weight 821.14 g/mol, GE Healthcare Buchler GmbH & Co.KG, Germany) and a solution consisting of visipacue® 54 %, DMSO — 10 %, polypropylene glycol 400 — 36 %. DMSO substances and polypropylene glycol are already used as an OBA. They were added to the visipacue® for testing the possibility of enhancing its clearing ability, shown in Ref. [5]. Hereinafter all substances used will be referred to as OBA. The evaluation of the effectiveness of OBA clearing in the area of the human nailbed *in vivo* was carried out using the OCT method by calculating the extinction coefficient when light propagates deep into the tissue. The lower the extinction coefficient, the more probing radiation will penetrate to great depths. Each OBA was applied to the nailbed of six healthy volunteers at a distance of two millimeters from the eponychium. Only one OBA was used for each finger. All the fingers were washed with ordinary soap before the experiments. Each OBA was applied to the area of the nailbed using a pipette. Imaging of the area under study using OCT was performed before applying the OBA to the skin, immediately after application, and then after 5 min for 15 min. After each act of OCT imaging, a tissue applicator moistened with OBA was applied to the area of application of the agent to prevent drying. Before recording the images, the remains of the OBA were carefully removed with a sterile cloth. The OBA was re-applied to the change area immediately after recording. The studied area was visualized using a GAN930V2-BU optical coherence tomograph (Thorlabs, USA) (wavelength 930 ± 5 nm, axial and lateral resolution 5.34 and $7.32 \mu\text{m}$, respectively) [5]. At the beginning of each five-minute time interval, five OCT recordings were performed for averaging for three regions located at a distance of no more than $500 \mu\text{m}$ from each other.

The attenuation coefficient was reconstructed with depth resolution using the method described in Ref. [8], taking into account optimization suggestions from the study [9]. The influence of the axial point spread function (APSF)

described in Ref. [10,11] was also preliminarily taken into account.

An adequate assessment of the optical properties of samples by optical coherence tomography (OCT) requires taking into account the influence of the axial point spread function $h(z)$ due to the characteristics of the optical system. The depth profile of the amplitude of the OCT signal ($i_s(z)$) is described by the following expression:

$$i_s(z)^2 \sim R_s(z) = h(z) \exp(-2\mu_t z), \quad (1)$$

where $R_s(z)$ is the reflection coefficient of the sample on the optical axis as a function of depth z , $h(z)$ is the scattering function of the axial point, $\mu_t(z)$ is the extinction coefficient.

The following function was proposed and tested to describe the axial point spread function in the context of OCT [11]:

$$h(d) = \frac{1}{\left(\frac{d}{z_i}\right)^2 + 1}, \quad (2)$$

where d is the distance of the reflecting object to the position of the focal plane, z_i is the Rayleigh length in the i -th layer of the sample.

The Rayleigh length is calculated using the formula:

$$z_i = \frac{\pi n \omega_i^2}{\lambda_0}, \quad (3)$$

where n is the group refractive index of the sample, ω_i is the radius of the constriction in focus (lateral resolution OCT), λ_0 is the central wavelength of the probing radiation OCT.

The equations (1)–(3) were used to reconstruct the deep profile of the reflection coefficient of the sample. The value of the Rayleigh length z_i was calculated using equation (3), where the refractive index of the sample was assumed to be $n = 1.41$.

The equation from Ref. [9] was used to reconstruct the deep profile of the extinction coefficient $\mu_t(z)$, taking into account the discreteness of the signal:

$$\mu_t(i) = \frac{I(i)}{2\Delta \sum_{i=1}^N I(i)},$$

where Δ is the pixel size, $I(i)$ is the OCT signal intensity of i -th pixel, N is the number of pixels in axial direction.

The effectiveness of optical clearing, was estimated based on changes in the extinction coefficient averaged over the depth in the skin of the nailbed in the ranges of 0–50, 100–200, 300–400 μm and calculated based on two-dimensional OCT images (Fig. 1).

Results and discussion

Fig. 2 shows the results of a study of the effect of various (OBA) on the tissues of the human nailbed. OCT-images of the tissue area obtained before the application

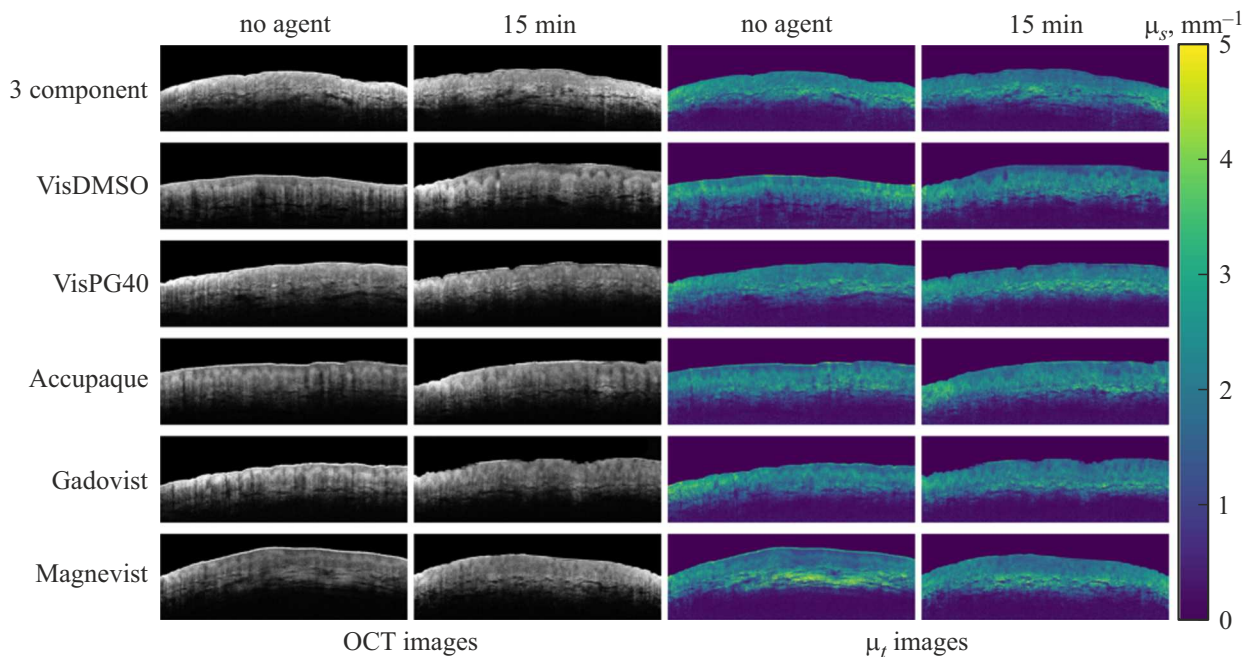


Figure 2. OCT images (left part) and extinction coefficient maps (μ_t) (right part) for various OBA: three-component solution (3Component), VisDMSO (90 % visipacue®, 10 % DMSO), VisPG40 (40 % visipacue®, 60 % polypropylene glycol), Accupaque, Gadovist and Magnevist. The results are shown before the application of the agent (no agent) and 15 min after the application (15 min). Maps μ_t visualize the spatial distribution of the extinction coefficient.

of the agent (no agent) and 15 min after its application. The images show a change in tissue structure in response to the use of various OBA. Attenuation coefficient maps (μ_t) calculated for the same time points. These maps visualize the spatial distribution of changes in the extinction coefficient, which makes it possible to quantify the decrease in light scattering. The most pronounced decrease in the extinction coefficient is observed when using a three-component solution (3Component) and a mixture of visipacue and propylene glycol (VisPG40). A smaller clearing effect is observed for the magnevist and gadovist, which is confirmed by a less pronounced change in the attenuation coefficient maps. Maps of μ_t -coefficient on the right side of the figure show that the effectiveness of optical clearing is most noticeable in the surface layers of tissues (0–50 μm).

Figure 3–5 shows the extinction coefficients, normalized to the initial value before applying the OBA, calculated and averaged for depths in the ranges of 0–50, 100–200, 300–400 μm of the nailbed, depending on the type of OBA used and the time elapsed after their application. The data are divided for OBA with RO substances and with MR substances. The optical clearing effect for the depth range of 0–50 μm can be observed in Fig. 3. Vizipak® and polypropylene glycol solutions, as well as a three-component solution demonstrated the highest optical clearing efficiency. The decrease relative to the initial values was $30 \pm 13\%$ and $32 \pm 18\%$, respectively, at the 15-th min of measurement. The accupacue® showed a worse result, with a decrease of $16 \pm 10\%$. The effect of clearing is weaker for MR

substances. For instance, after 15 min from the application of the substance, the extinction coefficient dropped by $16 \pm 8\%$ in case of usage of gadovist® and by $20 \pm 15\%$ in case of usage of magnevist®.

The results of reducing the extinction coefficient for the depth range of 100–200 μm are shown in Fig. 4. The greatest decrease in the extinction coefficient is observed in case of usage of a three-component solution ($16 \pm 7\%$). The remaining samples with visipacue® and accupacue® reduce the extinction coefficient by $7 \pm 5\%$. Magnevist® and gadovist® show a similar decrease by $8 \pm 6\%$. It was shown that there is no optical clearing effect at depths of 300–400 μm (Fig. 5). We believe that the lack of an optical clearing effect for both groups of used substances in this range is due to the lack of penetration of the used substance to the specified depths.

Conclusion

The selected substances reduce the coefficient of tissue extinction in the area of the human nailbed, which means they are effective for optical clearing. The greatest clearing effect is observed at the depth range of 0–50 μm . This means that they can be used to visualize the capillaries of the nailbed using digital capillaroscopy, which visualizes capillaries using depth data [12]. However, MR agents proved to be less effective compared to solutions of the RO agent visipacue®. A three-component solution consisting of 54% of visipacue®, 10% of DMSO, and 36% of

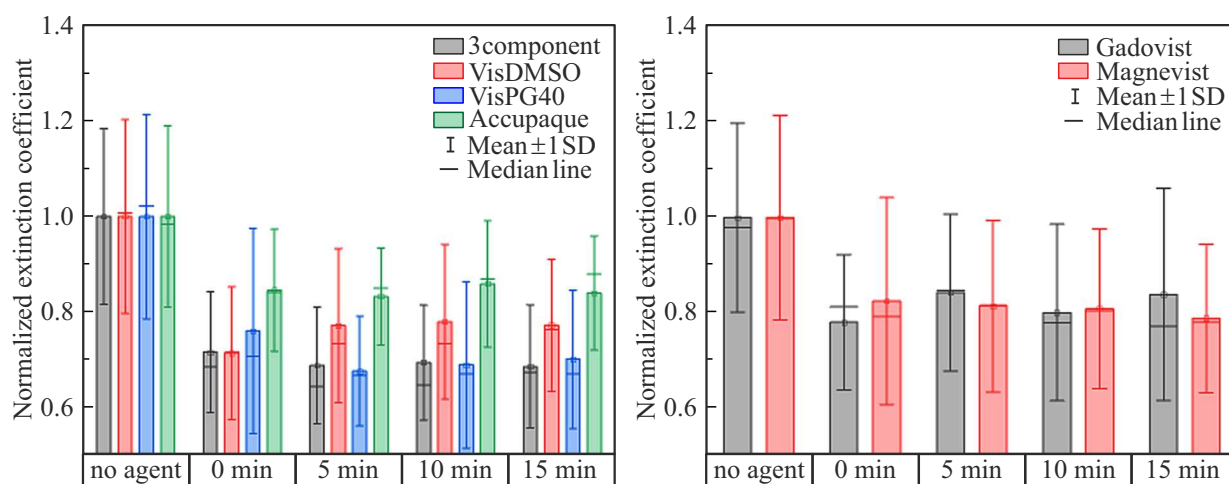


Figure 3. Dependences of extinction coefficients on the time after application of OBA at moments 0 and after 5, 10 and 15 min, respectively, averaged in the depth range 0–50 μm for OBA with RO substances (on the left) and for MR agents (on the right). VisDMSO — visipacue mix[®] 90 % and DMSO 10 %, VisPG40 — a mixture of visipacue[®] 40 % and polypropylene glycol 400 60 %, 3Component — a solution consisting of visipacue[®] 54 %, DMSO 10 %, polypropylene glycol 36 %. No agent — before application of OBA, 0 min — measurement immediately after application of OPA. SD — standard deviation.

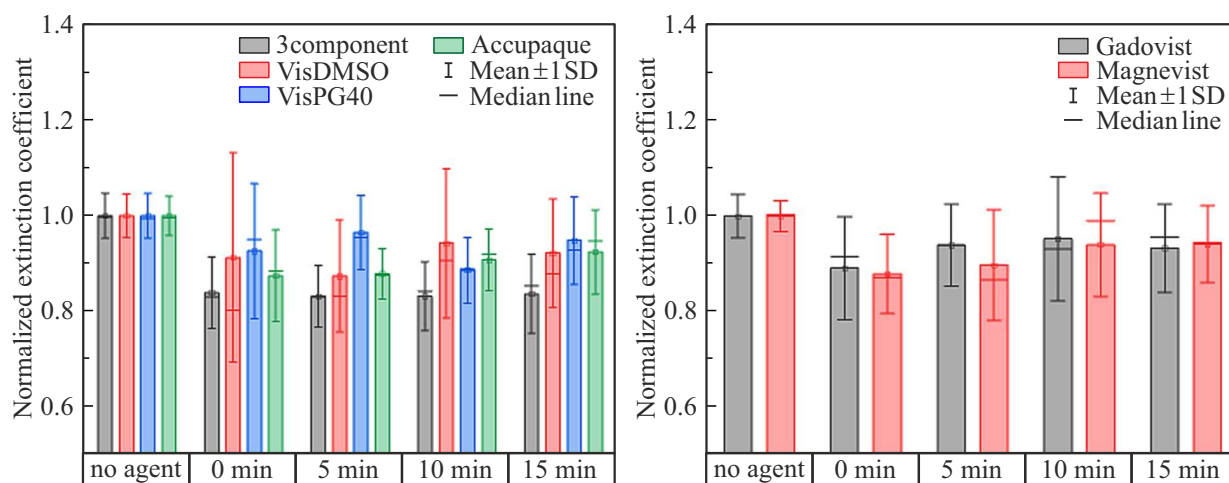


Figure 4. Dependences of extinction coefficients on the time after applying the OBA at moments 0 and after 5, 10 and 15 min, respectively, averaged in the depth range of 100–200 μm for OBA with RO substances (on the left) and for MR agents (on the right). VisDMSO — visipacue mix[®] 90 % and DMSO 10 %, VisPG40 — a mixture of visipacue[®] 40 % and polypropylene glycol 400 60 %, 3Component — a solution consisting of visipacue[®] 54 %, DMSO 10 %, polypropylene glycol 36 %. No agent — before application of OBA, 0 min — measurement immediately after application of OPA. SD — standard deviation.

polypropylene glycol turned out to be the most effective OBA for enhancing light penetration. We assume that the effect of optical clearing is also related to the effect of dehydration of the tissue under study. As a result of this process, the scattering centers are arranged more compactly, which reduces the multiple scattering of light [3].

Compliance with ethical standards

All the volunteers gave written informed consent to participate in the experiment. Experiments involving humans were approved by the local Ethics Commission

of the Lomonosov Moscow State University No. 6/23 dated 16.10.2023.

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Conflict of interest

The authors declare that they have no conflict of interest.

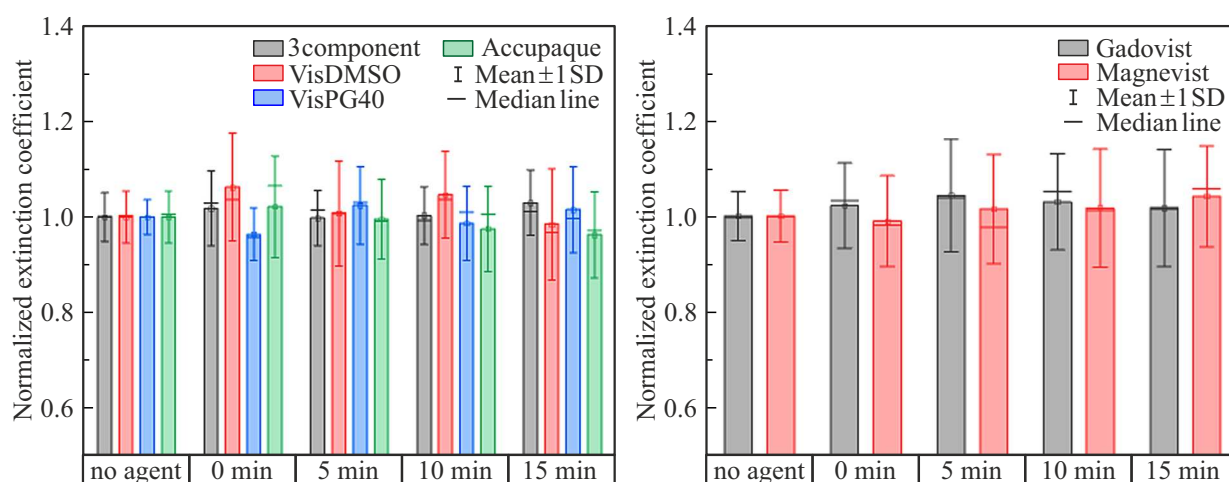


Figure 5. Dependences of extinction coefficients on time after application of OBA at moments 0 and after 5, 10 and 15 min, respectively, averaged in depth range 300–400 μm for OBA with RO (on the left) and for MR agents (on the right). VisDMSO — visipacue mix[®] 90% and DMSO 10%, VisPG40 — a mixture of visipacue[®] 40% and polypropylene glycol 400 60%, 3Component — a solution consisting of visipacue[®] 54%, DMSO 10%, polypropylene glycol 36%. No agent — before application of OBA, 0 min — measurement immediately after application of OPA. SD — standard deviation.

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