Light distribution in the endometrium during photodynamic therapy

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ABSTRACT

Hysterectomy is the most common major operation performed in the United States with dysfunctional uterine bleeding being a major indication[1]. Endometrial destruction by photodynamic therapy (PDT) has been suggested as a possible alternative to invasive surgical procedures for abnormal uterine bleeding due to benign changes.

Effective destruction of the endometrium during PDT requires a sufficient amount of light to be delivered to the entire endometrium in a reasonable time. To satisfy these criteria, we have developed a trifurcated optical applicator consisting of three cylindrical diffusing fibers. The applicator was inserted into freshly excised, intact human uteri and the optical distribution was measured with an isotropic fiber probe at various locations in the uterus. The results were in good agreement with the predictions of a mathematical model based on diffusion theory. The results indicate that irradiation of the endometrium by the trifurcated applicator can destroy tissue to a depth of 4 mm given an optical power of 100 mW per cm of diffusing tip (100 mW/cm) for an exposure time of less than 20 minutes.

2. INTRODUCTION

The endometrium is a highly vascularized tissue layer lining the uterine cavity (Figure 1). Its thickness varies between 2 and 6 mm depending on the stage of the menstrual cycle. The endometrium is surrounded by a relatively thick (ca. 15 - 30 mm) muscular layer termed the myometrium. Although the uterus is a hollow organ, it is normally collapsed. Dysfunctional uterine bleeding is a common affliction among women between the ages of 25 and 54[1]. In many cases this condition is remedied by the removal of the uterus. The results of several animal studies[2-5] have shown that selective destruction of the endometrium using PDT may provide a viable alternative to hysterectomy. Various photosensitizers administered both systemically and topically have been considered, however, topical administration is preferred due to the problem of skin photosensitivity associated with systemically administered photosensitizer. In order to prevent regeneration of the endometrium, a sufficient amount of light must be delivered to the entire endometrium and the innermost layer of the myometrium[6]. To address this issue, a trifurcated optical applicator was inserted into freshly excised human uteri and the fluence rate was measured at various locations. The results were compared to predictions of diffusion theory.

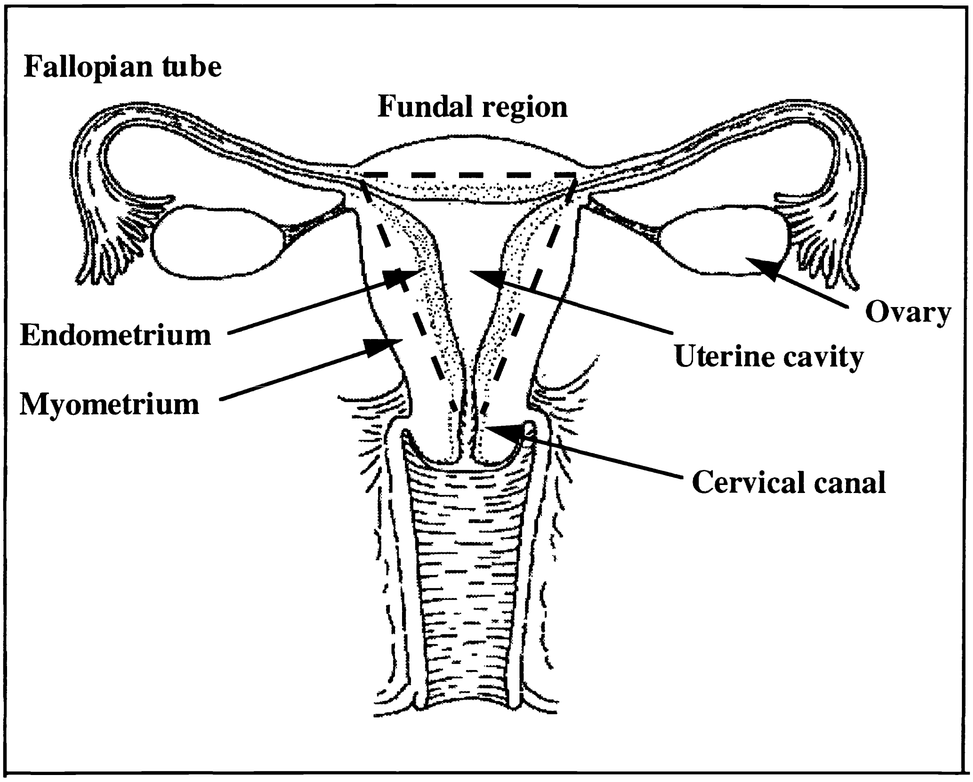

Figure 1. The human uterus. The dashed lines mark the boundary of destruction.

3. THEORY

In most instances, the light distribution in biological tissues can be adequately described by the diffusion equation:

$$\nabla^2\varphi - \frac{\varphi}{\delta^2} = -\frac{q}{D}c \tag{1}$$

where φ is the optical fluence rate, c is the velocity of light in the tissue (assuming a refractive index of 1.40), q is the diffuse photon source density and D is the optical diffusivity:

$$D = \frac{c}{3(\mu_a + \mu_s')} \tag{2}$$

where μ_a and μ'_s are the optical absorption and reduced scattering coefficients respectively. The optical penetration depth is given by:

$$\delta = \sqrt{\frac{D}{c\mu_a}} \tag{3}$$

Normally, the cavity of the uterus is collapsed and has a triangular shape (Figure 1).The expression for the fluence rate in the cylindrical symmetric case where a long cylindrical applicator is positioned coaxially in the uterine cavity has been given by Svaasand et al[7]:

$$\varphi = \frac{P\delta c}{2\pi a D K_1\left(\frac{a}{\delta}\right)} K_0\left(\frac{r}{\delta}\right) \tag{4}$$

where P is the optical power per unit length of the applicator, a is the radius of the cylindrical cavity, r is the distance from the axis and K_0 and K_1 are the modified Bessel K-functions of zeroeth and first order.

4. MATERIALS AND METHODS

Intact uteri were obtained immediately following hysterectomy and placed on ice. In order to keep the optical properties as close as possible to the in-vivo situation, all major vessels of the uterus were closed by sutures prior to removal. Measurements were performed on a total of 12 specimens (9 pre- and 3 post-menopausal). During the measurement period (typically 3-4 hours), wet gauze was applied to the uterus to prevent dehydration. Samples were returned to the pathologist for tissue analysis following the measurements.

The fiber applicator consisted of three optical fibers with 30 mm long (1.2 mm dia.) cylindrical diffusing tips (PDT Systems, Inc., Santa Barbara, CA) affixed to an intrauterine device for support. Light (λ = 630 nm) from an argon-ion-pumped dye laser was coupled into an optical fiber which was connected to a three-way fibersplitter (PDT Systems, Inc., Santa Barbara, CA). The ends of the three cylindrical fibers were connected to the fibersplitter. With all fibers illuminated, the emitted optical power from each fiber was approximately 100 mW/cm (300 mW total power per fiber).

The experimental setup is illustrated in Figure 2. The cylindrical applicator was inserted through the cervical canal and a 200 μm core dia. (0.8 mm o.d.) isotropic detector fiber (PDT Systems, Inc., Santa Barbara, CA) was inserted through the uterine wall. The end of the fiber was connected to a photomultiplier tube (Hamamatsu R928, Bridgewater, NJ). A channel for the detector fiber was made by inserting a small gauge needle into the tissue. The needle was retracted and the detector fiber was inserted into the channel. Positioning of the detector fiber with respect to the cylindrical applicator was visually verified by using a 3 mm dia. rigid hysteroscope placed in the uterus. The detector fiber was retracted in a direction normal to the axis of the cylinder and the position was monitored by micrometer readings. The readings for the first 3-4 mm from the fiber were from the endometrium whereas readings from larger distances corresponded to the myometrium. In most cases, the lumen of the uterus was collapsed during the measurements. A series of measurements were performed to determine the effect of uterine distension on the fluence rate. The fluence rate was monitored at 2 and 6 mm depths from the uterine wall when 9 ml of a high viscosity, optically clear liquid (Hyskon®, Pharmacia, Inc., Piscataway, NJ) was injected into the uterine cavity.

The detector probe was calibrated in water with the use of a 7.2 mW (λ = 633 nm) HeNe laser. The emitted optical power from the cylindrical fibers were evaluated by inserting them into an integrating sphere and comparing the signals with those obtained from the HeNe laser.

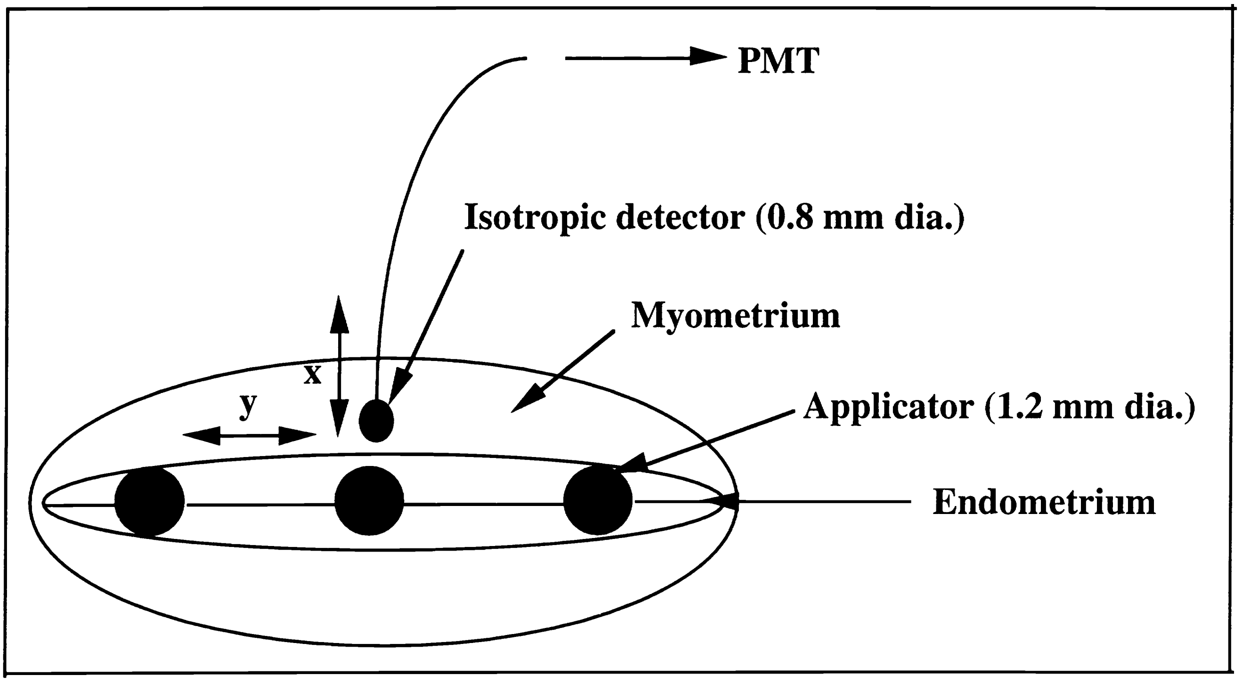

Figure 2. Schematic (end view) of experimental setup used to measure fluence rates.

5. RESULTS AND DISCUSSION

The fluence rate as a function of distance from the applicator axis is shown in Figure 3. The solid line represents the predicted fluence rate in the case of an infinitely long, 1.2 mm dia. cylindrical diffusing fiber with an emitted optical power of 100 mW/cm (equation (4)). A penetration depth of 4 mm (μ_a = 0.025 mm^{-1} and μ'_s = 0.8 mm^{-1}) was chosen based on previous measurements of pre-menopausal uteri[8]. There is good agreement between the measured and calculated values with the maximum deviation found in the boundary layer between the endometrium and myometrium (at 4 - 6 mm depth) being about 35 % (Series 3). The precision of the dosimetry model could be improved if the calculated values were based on in-situ measurements in the relevant case, i.e., by using non-invasive measurements based on photon migration techniques[8].

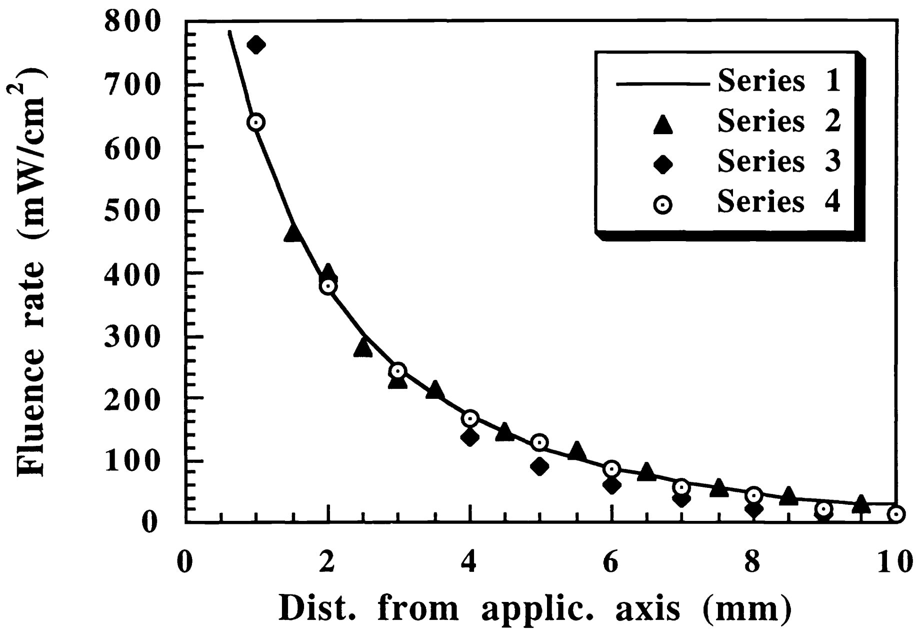

Figure 3. Fluence rate vs. distance from the applicator axis. Series 1: calculated values for an infinitely long applicator. Series 2 and 4: pre-menopausal uteri measured in the plane through the middle of the applicator. Series 3: pre-menopausal uterus measured in the plane through the end of the applicator. Measured values were multiplied by a factor of 2 to compensate for the semi-infinite geometry. In all cases, the applicator power was 100 mW/cm.

The most critical region for obtaining an adequate fluence rate is in the region where the distances between the fibers are maximal, i.e., in the fundal region. In order to determine the optimal applicator geometry required to achieve an adequate light distribution in the uterine cavity, a series of fluence rate measurements were performed in an average size pre-menopausal uterus with two and three fibers illuminated (Figures 4 and 5). The worst case scenario is illustrated in Figure 4a, i.e., the two illuminated cylindrical fibers lie along the outer edges of the uterine cavity. Fluence rate measurements were made at two locations: (1) at the end of applicator 1 at a depth of 2 mm into the uterine wall (denoted by the asterisk in Figure 4a) and, (2) approximately in the middle (ca. 2 - 5 mm from the origin) of the two applicators at a depth of 2 mm (denoted by the filled circle in Figure 4a). The fluence rate directly above fiber 1 was approximately 10 times that measured between the two fibers. The calculated fluence rate (Figure 4b) directly above fiber 1 was 10 - 30 times that calculated at the measurement position between the two fibers.

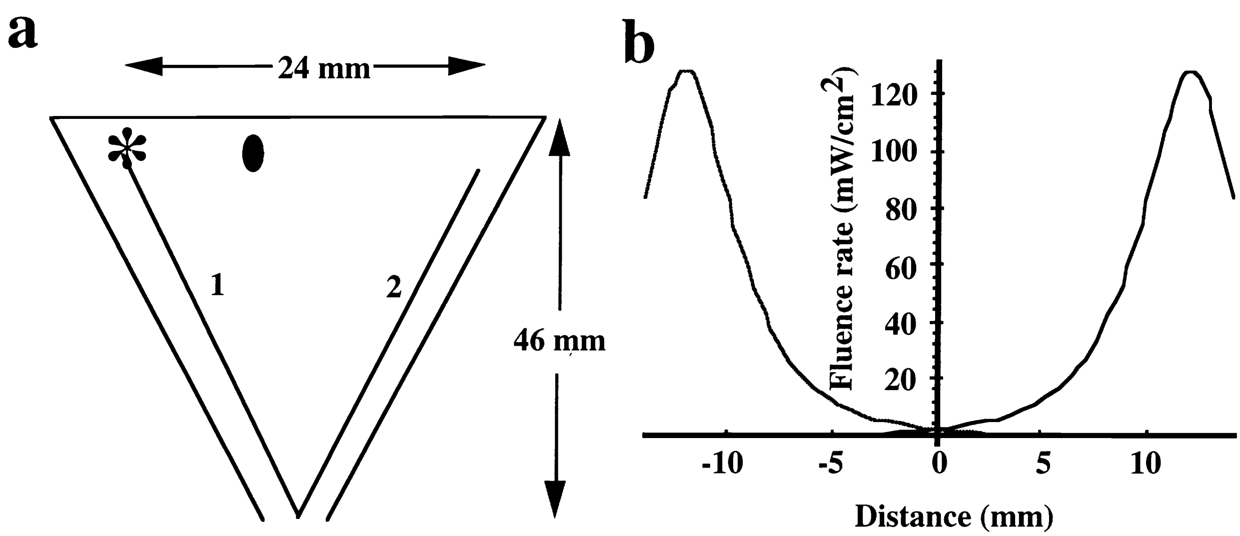

Figure 4. Fluence rates at 2 mm depth in the case of two illuminated fiber applicators. (a) Overhead view showing the positions of the detector probe relative to the fiber applicators. P = 100 mW/cm for each applicator. (b) Calculated fluence rate based on a measured δ of 2.8 mm and P = 100 mW/cm/applicator.

The case of three illuminated fibers is illustrated in Figures 5a and b. As before, measurements were made at a depth of 2 mm into the uterine wall. The measurement locations are denoted by an asterisk and a circle (Figure 5a). The fluence rate directly above fiber 3 was approximately 1.7 times that measured between fibers 1 and 3. For the calculated fluence rate (Figure 5b), the detector probe was positioned approximately 4 - 7 mm from the origin. The calculated fluence rate directly above fiber 3 was thus 2.9 - 3.9 times that calculated between fibers 1 and 3.

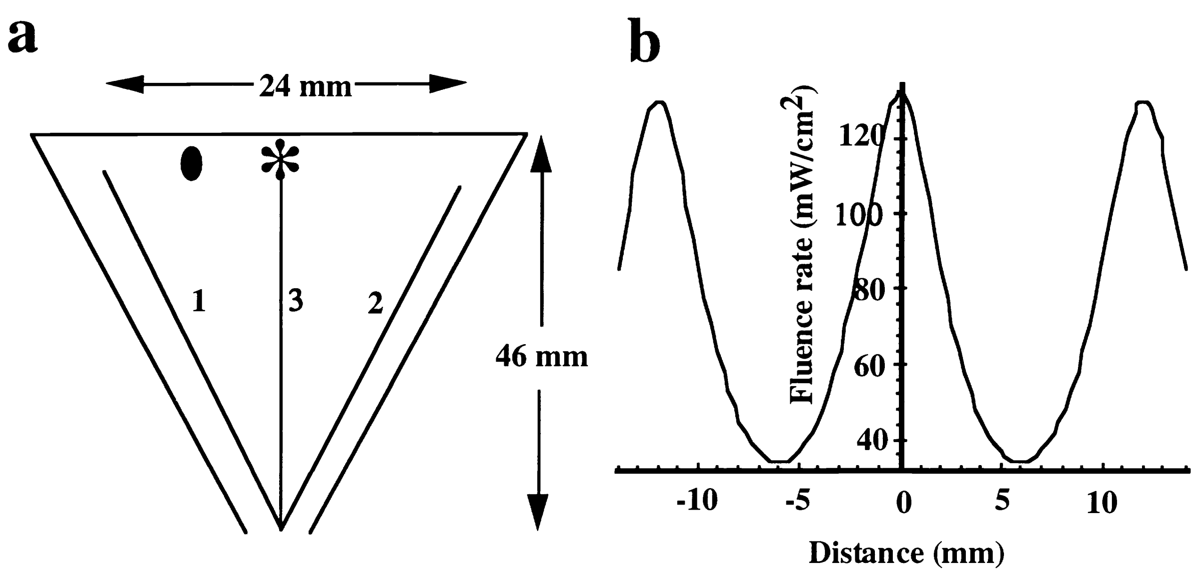

Figure 5. Fluence rates at 2 mm depth in the case of three illuminated fiber applicators. (a) Overhead view showing the positions of the detector probe relative to the fiber applicators. P = 100 mW/cm for each applicator. (b) Calculated fluence rate based on a measured δ of 2.8 mm and P = 100 mW/cm/applicator.

The large spreads in the calculated ratios were attributed mainly to uncertainties in the positioning of the detector and applicator fibers even though extreme care was exercised in verifying the fiber positions with a hysteroscope. Considering the difficulties associated with positioning the fibers, the fact that the measured and calculated fluence rate ratios agreed to within a factor of two suggests that the simple model used in this study is adequate.

In order to determine the time required to deliver an adequate light dose to destroy the entire endometrium, the fluence rate was calculated at a depth of 4 mm (corresponding to the thickness of an average endometrium) using identical fiber arrangements as illustrated in Figures 4a and 5a. The results are shown in Figure 6. The minimum fluence rates in the case of two and three illuminated fibers are approximately 1.7 (at the origin) and 23 (at -6 and +6 mm) mW/cm^2 respectively. Since the bleaching fluence for Protoporphyrin IX (generated by 5 - Aminolevulinic acid (ALA)) is approximately 50 J/cm^2, a dose of ca. 70 J/cm^2 should be delivered at a depth of 4 mm[7]. This would require ca. 51 min. of irradiation in the case of three illuminated fibers and, ca. 13 hrs. in the case of two fibers. Clearly, two fibers are inadequate to destroy the endometrium in a reasonable time. From a clinical point of view, the treatment time should not exceed 30 minutes. This goal may be achievable with the three fiber arrangement by increasing the applicator power by a factor of two. An applicator power of 200 mW/cm would result in a temperature rise of 4 - 5 ^{o}C at the optical penetration depth (2.77 mm in this case)[7]. This is just below the hyperthermic threshold.

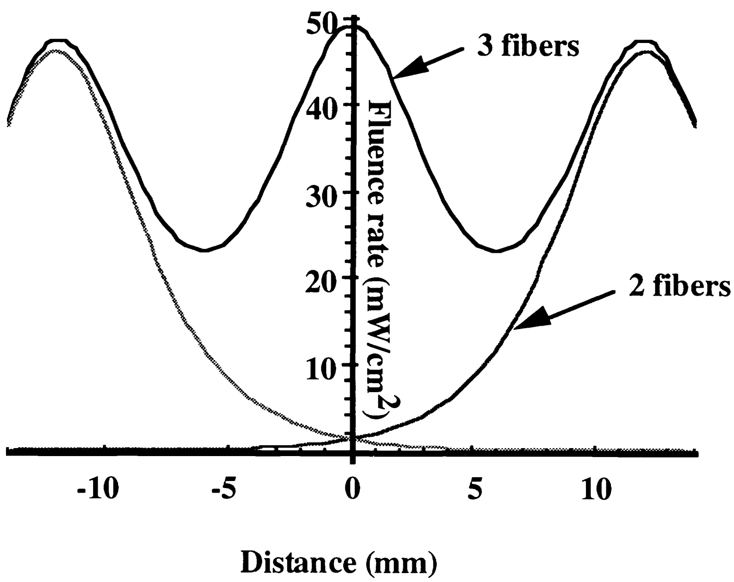

Figure 6. Calculated fluence rates for 2 and 3 fiber applicators at a depth of 4 mm. $\delta = 2.8$ mm and P = 100 mW/cm/applicator.

The fluence rate may be improved significantly by distending the uterine cavity resulting in an optically integrating cavity in which the fluence rate builds up due to light scattered back from the uterine wall. This was verified experimentally in a setup where all three fibers were radiating. The fluence rate was monitored at a depth of 2 and 6 mm from the uterine wall in the fundal region when 9 mL of a high viscosity, optically clear liquid (Hyskon®, Pharmacia, Inc., Piscataway, NJ) was injected into the uterine cavity in 1 mL increments (Figure 7). The fluence rate increased typically by a factor of 10 - 15 after injection of 9 mL of liquid. In a clinical situation, the amount of Hyskon® which can be injected is limited to beween 3 and 5 mL due to patient discomfort and spillage[9]. This suggests that the fluence rate could be enhanced by a factor of ca. 10 at a depth of 4 mm (Figure 7).

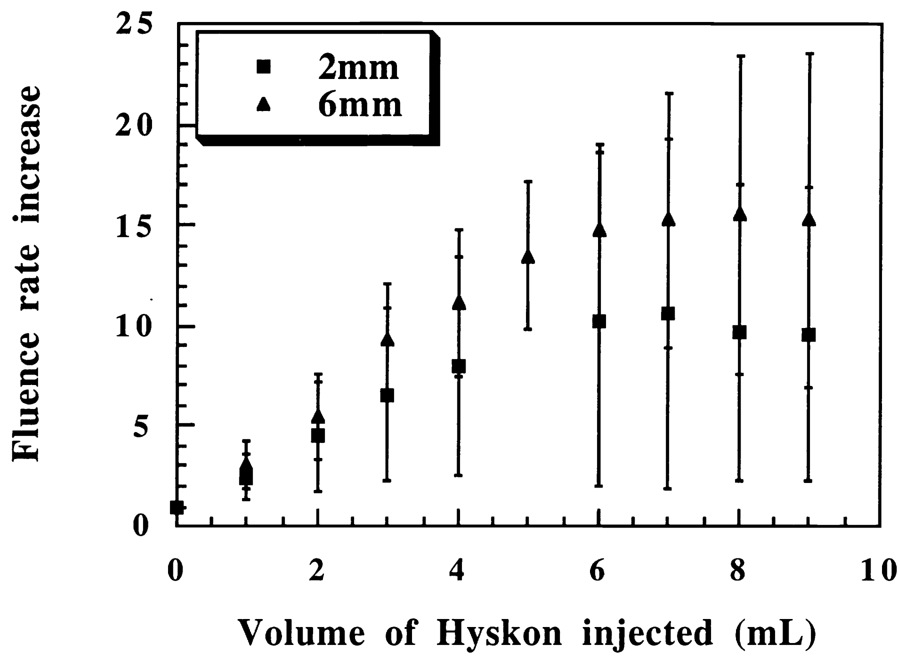

Figure 7. Increase in fluence rate as a function of injected Hyskon®. Each data point represents the average of three measurements performed on three different uteri.

6. CONCLUSIONS

The results of this study suggests that a sufficient light dose can be delivered to the entire endometrium of an average size uterus in less than 30 minutes without thermal damage using a trifurcated optical applicator consisting of three cylindrical diffusing fibers. The treatment time may be reduced significantly by distending the uterine cavity through injection of an optically clear, viscous fluid, such as Hyskon®.

7. ACKNOWLEDGEMENTS

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