High Injection Pressure During Intralesional Injection of Corticosteroids Into Capillary Hemangiomas

James E. Egbert, MD; Saurav Paul, PhD; W. Keith Engel, MD; C. Gail Summers, MD

Background: Intralesional injection of corticosteroids is an effective treatment for tumors of the head and neck. Complications are rare but include permanent loss of vision. We designed a study to investigate the mechanism for this complication.

Methods: Three fellowship-trained pediatric ophthalmologists participated in the study in a nonmasked fashion. Four patients received 5 separate treatment sessions of an intralesional injection of a 50-50 mixture of triamcinolone diacetate (40 mg/mL) and betamethasone sodium phosphate and betamethasone acetate (6 mg/mL) into capillary hemangiomas. Injection pressure was obtained in real time using a cannula designed for this purpose. Maximum pressure, mean pressure, and volume of corticosteroid were measured from each injection.

Results: A total of 71 injections (range, 8-33 injections per patient) was performed. The total volume of corticosteroid ranged from 0.9 to 2.1 mL. In 63 of 71 injections, the maximum pressure exceeded 100 mm Hg (range, 18.65-842.18 mm Hg). Each surgeon produced injection pressures greater than the systemic arterial pressures of each patient.

Conclusions: Injection pressures exceeding the systemic arterial pressures routinely occur during intralesional injections of corticosteroids into capillary hemangiomas. Experienced surgeons participating in a nonmasked protocol were unable to prevent high injection pressures of corticosteroid. A sufficient volume of corticosteroid injected at high injection pressure would account for the embolization of corticosteroid particles into the ocular circulation from retrograde arterial flow. We recommend limiting the volume of corticosteroid and performing indirect ophthalmoscopy on all patients receiving injections of long-acting corticosteroids into the orbit and periorbital soft tissue.


INTRALESIONAL injection of corticosteroids is an effective treatment for a variety of benign and malignant proliferations in the head and neck regions. These disorders include chalazion, capillary hemangiomas, histiocytosis, nasal polyps, chronic nasal turbinate inflammation, and postrhinoplasty scarring. Unfortunately, intralesional injection of corticosteroid in the head and neck area can result in ocular embolization with permanent loss of vision. The mechanism for this complication has been hypothesized to be retrograde flow of injected drug from the target tissue into the ophthalmic artery proximal to the central retinal artery.

Ocular embolization from retrograde flow during injection of corticosteroids into capillary hemangiomas has been previously demonstrated in humans. For retrograde flow to occur, the injection pressure of corticosteroid would need to exceed the systemic arterial pressure.

The mechanism of ocular embolization from retrograde flow during intralesional injections of corticosteroids has not been studied. The absence of an acceptable animal model for capillary hemangiomas and lack of a device to measure in situ pressure and drug volume applied during intralesional injection of corticosteroids have prevented in vivo studies.

We have designed a custom device that allows simultaneous measurement of injection pressure and volume for use during intralesional injection of medications. The accuracy of this device has been verified by studies with an animal model simulating capillary hemangioma. The purpose of this article is to report the frequent occurrence of high injection pressures during intralesional injection of corticosteroids into capillary hemangiomas. The critical role of high injection pressure in causing retrograde flow of drug and the conditions under which retrograde flow of drug can lead to ocular embolization has not been investigated.
METHODS

MEDICATION

The corticosteroid drug used in this study was a 50-50 mixture of (1) triamcinolone diacetate (40 mg/mL Aristocort Forte; Fujisawa Pharmaceutical Co, Deerfield, Ill) and (2) betamethasone sodium phosphate and betamethasone acetate (6 mg/mL Celestone Soluspan; Schering Co, Kenilworth, NJ). A sterile suspension of this medication was found to remain constant at 0.0017 Pa s (pascal-second). The density of the mixture was 1.0 g/mL. The particle size distribution of this medication is 7% for a greater than 20-µm diameter. The viscosity of the mixture was measured using a cone-and-plate viscometer. At shear strain rates greater than 1.0 s⁻¹, the viscosity was found to remain constant at 0.0017 Pa s (pascal-second).

The density of the mixture was 1.0 g/mL⁻¹.

INSTRUMENTATION

The pressure produced during injection of corticosteroid was estimated by means of a specially designed cannula (Figure 1). The cannula was connected to a 3-mL non-pyrogenic disposable syringe (Monoject; Sherwood Medical, St Louis, Mo) filled with corticosteroid. The cannula was a standard 21-gauge stainless steel tube, 3.82 cm long, with a nominal internal diameter of 0.05 cm, and a sharp beveled tip at its distal end. The cannula was made with side ports for piezometric tappings at 2 sites along the length of the tube. The tissue pressure, "P₃," was calculated from pressures "P₁," and "P₂," measured at these 2 side ports. The flow of the drug mixture in the syringe-cannula injection system was modeled as a steady-state laminar flow of homogeneous particulate suspension. The relationship between pressure drop and flow rate was established from the Poiseuille law in conjunction with the Bernoulli theorem. Under in vivo conditions of injection, the backpressure P₁ existing at the tissue at the site of injection was taken to be the same as the pressure at the outlet tip of the cannula. The tissue equilibrium pressure was the value of P₁ when flow rate just exceeded zero at the start of the injection.

The pressure signal was acquired and measured using techniques validated in vitro and in vivo. In brief, the side ports of the cannula were connected to the transducers by polyethylene tubing filled with water to maintain fluid coupling. The pressure transducers were connected to a signal-conditioning amplifier (model 563HL; Ectron Co, San Diego, Calif) and the calibrated signal was acquired digitally into the computer at a sampling frequency of 10 Hz. The signal-conditioning amplifier and the analog-to-digital acquisition system were configured to allow pressure measurements at a digital resolution of 0.488 mm Hg. The data acquisition, processing, and on-line computer display were achieved by software developed using LabVIEW (National Instruments, Austin, Tex) programming language.

RESULTS

Three pediatric ophthalmologists performed injections during the study. Four patients were studied, 2 patients...
received a single treatment session, and 2 patients received 2 treatment sessions. All sessions were included in the study except for the second session of a single patient. This omission occurred because of a conflict in scheduling the computer system.

A typical waveform generated during injection is shown in Figure 2. The data for each patient are presented in Tables 1, 2, 3, 4, and 5. A total of 71 injections was performed, and only 8 were at pressures less than 100 mm Hg. The maximum pressures ranged from 18.65 mm Hg to 842.18 mm Hg. All 3 pediatric ophthalmologists produced pressures greater than the systemic arterial pressure of each patient. No reduction of ocular circulation or emboli was observed during or following the injections.

**CASE 1**

A healthy 4-week-old girl had a cutaneous and subcutaneous capillary hemangioma of the temporal third of the right upper eyelid and superior temporal quadrant of the orbit. During the next 4 weeks, the capillary hemangioma completely obstructed the pupil. At 8 weeks of age, the patient received a total of 1.34 mL of corticosteroid injected at 8 separate sites (Table 1). The maximum pressure during the injections ranged from 36.24 mm Hg to 490.80 mm Hg. Only 3 of the 8 injections were performed with a maximum injection pressure of less than 100 mm Hg. The visual axis cleared within 2 weeks following injection. At 19 months of age, the visual acuity was equal, alignment was orthophoric, and no anisometropic refractive error was present.

**CASE 2**

A healthy 4-month-old infant had a subcutaneous lesion of the left superior nasal orbit that produced a bluish tinge to the overlying skin. At 6 months of age, the medial aspect of the left upper eyelid was encroaching the pupil, and the left eye had amблиопия due to 4.5 diopters (D) of astigmatism. At that time, the patient underwent an incisional biopsy revealing a capillary hemangioma, for which she received an injection of 1.09 mL of corticosteroids divided into 9 separate sites (Table 2). The maximum pressure during each injection ranged from 18.65 mm Hg to 649.60 mm Hg. Four of the 9 injections were performed with a maximum injection pressure of less than 100 mm Hg. Following injection of corticosteroid, the visual axis cleared, but 4 D of astigmatism remained. Two months later, the patient received a second intralesional injection of corticosteroid without pressure recording. At 27 months of age, the visual acuity was 20/30 in each eye, with 1.75 D of astigmatism in the left eye.
A healthy 2-month-old boy was referred for evaluation of a swelling of the nasal portion of the left upper eyelid. A subcutaneous mass creating a blue coloration to the skin was present. At 3 months of age, amblyopia was present, owing to 6.50 D of astigmatism. He underwent an incisional biopsy demonstrating a capillary hemangioma, and received an injection of 0.94 mL of corticosteroid divided into 8 different sites (Table 3). The maximum pressure during each injection ranged from 51.49 to 383.25 mm Hg. Only 1 of the 8 injections was performed with an injection pressure less than 100 mm Hg. During the next 2 months, a small decrease in the size of the capillary hemangioma occurred, but the refractive error did not change. At 7 months of age, 1.55 mL of corticosteroid was injected into the capillary hemangioma using 13 separate injections (Table 4). The maximum pressure during each injection ranged from 195.20 mm Hg to 405.60 mm Hg. At 33 months of age, the visual acuity was equal, and 4.5 D of astigmatism in the left eye remained. The capillary hemangioma was present but reduced in size.

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### CASE 3

A healthy infant girl was noted to have a right superior nasal orbital mass at 1.5 months of age. At 3 months of age, the pupil was partially obstructed by a subcutaneous mass, producing a bluish tinge to the overlying skin. Examination of an incisional biopsy specimen confirmed a capillary hemangioma, and injections of 2.11 mL of corticosteroid divided into 33 different sites were performed (Table 4). The maximum pressure of each injection ranged from 149.0 mm Hg to 842.2 mm Hg. None of the 33 injections was performed at a maximum injection pressure of less than 100 mm Hg. At 7 months of age, the visual acuity was equal, and the capillary hemangioma had decreased in size.

### COMMENT

Three experienced, fellowship-trained, nonmasked pediatric ophthalmologists (J.E.E., W.K.E., and C.G.S.) routinely performed injections of corticosteroids into capillary hemangiomas at pressures greater than the systemic arterial pressures of the infants. This occurred despite each surgeon attempting to use the least amount of pressure nec-
necessary, and stopping the injection when told by the computer operator when injection pressures reached 100 mm Hg. The injection pressures we have measured are sufficient to cause retrograde flow into the orbital circulation. Retrograde flow is a necessary but not a sufficient condition to cause ocular embolization. In the presence of high injection pressure, ocular embolization can occur if a sufficient volume of a drug is injected into the vasculature. None of the study patients receiving intralosomal injections of corticosteroid had any retinal complications. We deduce that the lack of ocular embolization, despite frequent high injection pressures, was owing to the limited total and individual injection volume delivered.

Two necessary conditions for ocular embolization are retrograde flow, and a sufficient volume of corticosteroid delivered during an intralosomal injection. Retrograde flow can occur when the corticosteroid is injected either into a terminal artery that feeds the capillary hemangiomata, into the capillary bed, or into the interstitial space of the capillary hemangiomata. When the drug is injected directly into a terminal artery, retrograde flow will occur if the pressure of the injected corticosteroid exceeds the systolic arterial pressure and frictional losses owing to viscous flow of drug in the artery. Arterial pressure in mature infants averages 70/50 mm Hg and gradually increases with age.

The pressure drop due to the viscous flow of the drug within the arteriole can be approximated using the Poiseuille law:17,18,21,22 Using the axial distance of the medial orbit (4.5 cm) and a lumen diameter of 0.05 cm for an arteriole,23 the mean pressure drop from the eyelid to the apex of the orbit, at a mean flow rate of 4 mL/min, is 23 mm Hg. When the drug is injected into a terminal artery, the drug will predominantly flow in the direction of least resistance. The resistance to fluid flow in a terminal artery is much less than the resistance in capillaries.24,25

Retrograde flow of the drug from the eyelid toward the apex of the orbit could, therefore, occur if the surgeon inadvertently injects corticosteroids into an arteriole at pressures exceeding the systemic arterial pressure. Retrograde flow into an arteriole can also occur if the medication is injected at high pressures into a capillary bed. The particle size distribution of the corticosteroid drug used in this study, namely, a 50-50 mixture of triamcinolone diacate and betamethasone sodium phosphate and betamethasone acetate, has been shown to remain unchanged for the short durations of injection.26 With the drug particle size predominantly smaller than the capillary diameter, retrograde flow can also occur if the medication is injected at high pressures into a capillary bed. When drugs are injected at pressures exceeding the arterial pressure, then, under the assumptions of uniform hydraulic conductivity of the drug within the tissue, the amount of drug flowing in the arterial and the venous directions will be directly proportional to the pressure gradients in the respective direction.27,28 For instance, in an infant with an arterial pressure of 70/50 mm Hg and a venous pressure of 10 mm Hg, injecting the drug at a pressure of 100 mm Hg midway between the artery and the vein will cause the flow to occur in the ratio of 0.48:1.00 in the arterial and venous direction. That is, 33% of the injected drug will flow in the retrograde direction. The percentage of drug displaced in the arterial direction will increase with increasing injection pressure.

Thus, percentages will be 43% at 200 mm Hg, 46% at 300 mm Hg, and they will asymptotically be 50% of the injected volume at very high injection pressures. In reality, the assumption of uniform hydraulic conductivity in tissues is, however, not strictly correct. Even in normal tissue, variability of the vessel size and distribution in the terminal vascular beds are known to cause appreciable changes in pressure gradients.24,25 Under pathological conditions, the morphological changes that occur in tissues and microvascular structures generally accentuate such inhomogeneities.29-31 This is especially true for capillary hemangiomata. Histopathological and ultrastructural examinations have revealed that capillary hemangiomata have areas of large vascular spaces with few endothelial cells, along with areas of densely packed endothelial cells and fibrous tissues with much less vasculature.32-33 This is further complicated by the possible vasoconstrictive effects of corticosteroids on vascular beds.34,36 As a result, the pressure drop at a distance from the injection site within a capillary hemangiomata cannot be accurately determined a priori to allow a margin of safety from overpressurization during injection of corticosteroids.

Retrograde flow alone is not sufficient to cause ocular embolization. For ocular embolization of corticosteroid during injection, the medication has to gain access to the ophthalmic artery proximal to the central retinal artery. This happens only when the following 2 conditions are met in sequential order: (1) high injection pressure necessary to cause retrograde flow of drug is established and (2) a sufficient volume of drug is injected at such high pressures. While high injection pressure occurs frequently, the volume of the drug necessary to cause embolization of the ocular circulation depends on a number of factors, including the proximity of the injection site from the ophthalmic artery proximal to the central retinal artery. For a feeder vessel from the ophthalmic artery arising just proximal to the central retinal artery and without branches, the minimum volume of drug necessary to cause embolization would be the amount needed to fill the arteriole. Using typical dimensions of an arteriole, as before (lumen diameter of 0.05 cm and axial distance of 4.5 cm for the medial orbit), the required volume is only 0.01 mL.23 The arterial network of the orbit is, however, complex, with many branches emanating from the ophthalmic artery.38 Calculating the volume of drug necessary for ocular embolization would require the formidable task of knowing the exact location of the injection site, its proximity to the feeder vessel, and the size, number, and distribution of the branching arterioles between the injection site and the ophthalmic artery adjacent to the central retinal artery.

The total volume of corticosteroid injected into a capillary hemangiomata also determines whether ocular embolization occurs when the drug is delivered into the interstitial space within the tumor. For injections into the interstitium of the capillary hemangiomata, fluid flow is significantly limited by the resistance offered by the surrounding normal tissue and the lack of a functioning lymphatic drainage system.39 Continued injection of the drug beyond the capacity of the extracellular space displaces the corticosteroid into venules and arterioles. At injection pressures higher than the systemic arterial...
pressure, this results in retrograde flow of the drug into arteries. The volume of the extracellular space within a tumor is, however, not known a priori. For solid tumors, the vascular space can range from 1% to 20% of the total volume.\textsuperscript{41,42} Capillary hemangiomas are vascular tumors, and the interstitium and vasculature should be expected to occupy a higher percentage of the tumor volume. Assuming a value of 30%, the total volume of drug that can be safely injected into a capillary hemangioma sized 3 × 2 × 1.5 cm (ellipsoid volume, 4.7 mL) is just 1.4 mL.\textsuperscript{43}

Other investigators have argued that the injection pressure can be maintained within safe limits by using a large-capacity syringe and small-bore cannula.\textsuperscript{43} Using Pascal’s law, Bullock et al.\textsuperscript{43} concluded that ocular explosions occurring from inadvertent high-pressure intraocular injection of anesthetic agents can be prevented with a sufficiently large syringe. Unfortunately, this will not prevent injection pressures from exceeding the systolic pressure of infants during intralesional injection into capillary hemangiomas. Pascal’s law states that pressure is inversely proportional to the cross-sectional area for any applied force. Accordingly, the digital force applied to the plunger of a large-capacity syringe will generate a lower pressure due to its increased cross-sectional area. The maximum force normally observed for a 3-point (palmar) pinch force is 11.4 kg for male adults, and 7.7 kg for female adults between ages 25 and 60 years.\textsuperscript{44} Using an unusually large syringe to inject 1 to 2 mL of drug, such as a 50-mL syringe with a plunger diameter of 2.5 cm, the corresponding pressures developed under hydrostatic condition are 1730 mm Hg and 1168 mm Hg, respectively, for male and female adults. Despite being lower than the reported values of 3000 mm Hg necessary to cause scleral rupture,\textsuperscript{45,46} these pressures are much higher than the pressure necessary to cause retrograde flow of drug into the ophthalmic artery.

Unfortunately, using a small-bore needle will not prevent high injection pressures. During injection of the drug, pressure losses occur from hydrodynamic effects of viscous flow within the cannula. Using the law of Poiseuille, the pressure drop due to viscous effects in the 21-gauge cannula is less than 21 mm Hg at a flow rate of 4 mL/min\textsuperscript{3}. Reducing the lumen diameter of the cannula by a factor of 2, as in the case of a 25-gauge cannula, can increase the pressure drop by 16 mm Hg to 336 mm Hg. Subtracting this pressure drop from the maximum pressure that can be exerted to a 50-mL syringe by female adults using a 3-point pinch force, a pressure of 832 mm Hg can still be obtained at the tip of the cannula. Clearly, such injection pressure far exceeds the systolic pressure in tissues.

The use of a large syringe and small needle will not prevent the surgeon who uses the least amount of pressure applied to the syringe from exceeding the systolic arterial pressure. Viscosity of the steroid medication increases at low flow rates and dramatically decreases with increasing flow.\textsuperscript{47} As a result, the resistance to flow of the medication through a needle is typically 10 times greater during initiation of the injection than when flow is established. Therefore, the surgeon needs to apply 10 times the amount of pressure to initiate flow than is necessary to maintain it. This higher initial pressure is directly trans-mitted to the tissue. The smaller the needle, the greater is the initial pressure transmitted to the tissues.

We have shown that a sufficient pressure is used during injection of corticosteroids into capillary hemangiomas to cause retrograde arterial flow. Our findings of routine high injection pressures of corticosteroids into capillary hemangiomas have direct implications to all physicians injecting corticosteroids into the orbital and periorbital regions. Surgeons cannot prevent high injection pressures by adjusting the size of the syringe or needle used during injection. Since high injection pressures will occur, limiting the volume of the corticosteroid, avoiding a direct intra-arterial injection, and avoiding placement of force to the treated tumor are the most important variables a surgeon can control. The following steps can be taken to minimize the risk of embolization of corticosteroids into the ocular circulation: (1) Before each injection of corticosteroid into the lesion, aspiration into the syringe should be performed to detect the presence of arterial blood. If blood is aspirated into the syringe, the cannula should be withdrawn and repositioned. If injections are performed without general anesthesia, steps to prevent movement of the needle tip during the time from aspiration to the end of injection are important. (2) Multiple areas of the capillary hemangioma should be treated with small volumes of corticosteroid. We agree with previous investigators\textsuperscript{52} that individual treatment sites receive 0.1 mL of medication. (3) The total volume of corticosteroid injected during the entire treatment session should be limited. We have found that total volumes of 0.8 mL to 1.5 mL were sufficient to cause shrinkage of periocular tumors between 4 mL and 8 mL in volume. (4) Because none of these efforts can completely prevent the occurrence of ocular embolization, we recommend indirect ophthalmoscopy be used during or immediately after treatment of lesions in the eyelid and orbital region. (5) Pressure to the tumor should not be applied, and a pressure patch should not be used, since these will increase the intratumor pressure and may dislodge corticosteroid into the arterial circulation. The child should not lay or sleep in a way such that the weight of the head is transmitted to the treated tumor. We recommend that a shield be placed for 24 hours around the tumor to prevent inadvertent pressure to the lesion.

Indirect ophthalmoscopy at the time of injection can immediately diagnose embolization of the ocular circulation. Embolization of the ophthalmic artery will result in a diffuse whitening of the retina and attenuation of blood perfusion in retinal arterioles. Embolization of the central retinal artery will produce the above effects, plus a “cherry” red spot in the fovea. Embolization distal to the central retinal artery will result in white glistening steroid particles visible in the retinal arterioles. In case of embolization of the ocular circulation, normal vision can be partially or fully salvaged with rapid treatment.\textsuperscript{10} This is essential since occlusion of the ocular circulation for more than 90 minutes results in necrosis of the retina.\textsuperscript{53} Treatment of ocular embolization involves the rapid reduction of intraocular pressure to promote dislodging the embolus into more peripheral branches of ocular circulation. This can be immediately performed by placing a needle or sharp cutting blade into the an-
terior chamber to decompress the intraocular pressure. In the absence of expertise, equipment, or restraint of the child to perform a mechanical decompression of the eye, massage of the eye can result in lowering of the intraocular pressure. Administration of carbonic anhydrase inhibitor and carbogen may also be used to treat ocular embolization of retinal arteries.

Several treatment modalities for capillary hemangioma exist.4 It is not the intention of this study to dissuade physicians from using intralesional injection of corticosteroids to treat capillary hemangiomas. Intralesional injection of corticosteroids into capillary hemangiomas can result in rapid clearing of the visual axis, resolution of induced astigmatism, and reduced amblyogenic potential.2 Many ophthalmologists commonly use this modality as the treatment of choice for capillary hemangiomas causing amblyopia.23,25 Ocular embolization is a rare complication probably because most physicians avoid an intra-arterial injection by aspiration before injection and limit the total and individual volume delivered per injection.23,25 Nevertheless, high injection pressures generated during injection increase the risk for retrograde flow and possible ocular embolization. Indirect ophthalmoscopy, during or after injections into the orbit and periorbital soft tissues, allows surgeons to immediately diagnose and treat this rare but serious complication.

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Corresponding author and reprints: James E. Egbert, MD, 440 Davis Ct, Suite 1111, San Francisco, CA 94111-2455.

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