Oxygen Therapy for Acute Ocular Chemical or Thermal Burns: A Pilot Study

FARIDEH SHARIFIPOUR, ALIREZA BARADARAN-RAFII, ESMAEIL IDANI, MITRA ZAMANI, AND MOHAMMAD HOSSEIN JABBARPOOR BONYADI

• PURPOSE: To evaluate the effect of systemic oxygen therapy in the management of acute ocular chemical and thermal burns.

• DESIGN: Prospective, nonrandomized, comparative, interventional case series.

• METHODS: Twenty-four eyes of 22 patients with grade III to IV acute ocular chemical and thermal burns received conventional medical therapy. The oxygen therapy group (13 eyes) additionally received 100% oxygen using a simple mask at a flow rate of 10 L/minute for 1 hour twice daily. Main outcome measures were time for healing of the corneal epithelial defect and improvement in perilimbal ischemia. Secondary outcome measures included visual acuity, corneal transparency and vascularization, and complications.

• RESULTS: Corneal epithelial defects healed within 15.23 ± 3.94 days (range, 10 to 21 days) in the oxygen group versus 59.9 ± 23.33 days (range, 28 to 95 days) in controls ($P < .001$). Vascularization of ischemic areas was complete in 14.54 ± 2.70 days (range, 10 to 21 days) in the oxygen group versus 45.09 ± 22.20 days (range, 25 to 105 days) in controls ($P = .001$). In the oxygen group, the cornea was more transparent and less vascularized 3 and 6 months after injury. Mean final visual acuity (logarithm of the minimal angle of resolution) was 0.40 ± 0.52 (range, 0 to 1.3) versus 1.11 ± 0.83 (range, 0.1 to 3) in the oxygen and control groups, respectively ($P = .018$). In the oxygen group, symblepharon or corneoscleral melting did not develop in any patient; however, in the control group, symblepharon developed in 3 eyes and corneoscleral melting developed in 1 patient.

• CONCLUSIONS: In the acute phase of ocular chemical or thermal burns, oxygen therapy improves limbal ischemia, accelerates epithelialization, increases corneal transparency, and decreases corneal vascularization. It also may improve visual acuity and reduce complications.

Accepted for publication Nov 3, 2010.

From the Department of Ophthalmology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (F.S., M.Z.); the Ophthalmic Research Center and Department of Ophthalmology, Shahid Beheshti University of Medical Sciences, Tehran, Iran (A.B.-R.); the Department of Pulmonology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (E.I.); and the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (M.H.J.B.).

Inquiries to Farideh Sharifipour, Department of Ophthalmology, Imam Khomeini Hospital, Azadegan Street, Ahvaz, Iran; e-mail: sharifipourf@yahoo.com, fsharifipour@ajums.ac.ir

(Am J Ophthalmol 2011;151:823–828.

OCULAR CHEMICAL AND THERMAL BURNS ARE true ophthalmic emergencies. The severity of the injury depends on the type of offending agent, its concentration, duration of exposure, and extent of contact.[1] Limbal stem cells, which are the source of corneal epithelial regeneration, are believed to be the most important potential targets in acute chemical burns.[1] The extent of limbal ischemia is considered to be the most important prognostic factor in determining final visual outcomes in these cases.[2,3]

Improving perilimbal ischemia and controlling inflammation theoretically can preserve partially damaged limbal stem cells. Promotion of epithelial healing, control of inflammation, and prevention of tissue melting are the main objectives in the management of acute ocular burns.[4] Persistent corneal epithelial defects may lead to tissue thinning or melting, perforation, and secondary infections. The de-epithelialized conjunctival surfaces tend to fuse and form symblepharon bands. Early conjunctival epithelial healing may prevent this complication.

With current medical therapies, smooth and complete conjunctivalization and vascularization of the cornea, without eyelid and adnexal structural abnormalities, are the optimal and acceptable goals in severe ocular burns. The ideal situation would be complete corneal conjunctivalization with minimal vascularization of the cornea. Conventional medical therapies, including steroids, ascorbate,[5,6] citrates,[6] tetracyclines,[7] lubricants, and surgical procedures such as application of a glued-on hard contact lens,[8] tenoplasty,[4] amniotic membrane transplantation,[9] have been used to achieve these goals.

The purpose of this study was to introduce systemic oxygen therapy as a novel therapeutic method in the acute phase of ocular chemical and thermal burns. By reducing perilimbal ischemia and decreasing inflammation, this method of therapy may facilitate epithelial healing and preserve partially damaged limbal stem cells.

METHODS

THIS PROSPECTIVE, COMPARATIVE, INTERVENTIONAL CASE series was performed at the Department of Ophthalmology,

0002-9394/$36.00
doi:10.1016/j.ajo.2010.11.005

Imam Khomeini Hospital, Ahvaz, Iran, and the Department of Ophthalmology, Labbafinejad Medical Center, Tehran, Iran. We included consecutive patients with grade III and IV (based on the Roper-Hall classification[10]) acute ocular chemical or thermal burns. Patients referred to the second study center served as the control group and received conventional medical therapy. The treatment group received systemic oxygen therapy in addition to conventional medical therapy on referral to the first study center, but no later than 3 weeks after injury. Oxygen was delivered at 100% concentration by a facial mask with flow rate of 10 L/minute for 1 hour twice daily in the sitting position. The 3-week window for giving oxygen was chosen arbitrarily to include more cases. Exclusion criteria included presentation later than 3 weeks after injury, inadequate treatment before presentation, history of ocular surgery or use of topical medications 1 month before injury, systemic immunosuppressive therapy, pregnancy, and contraindications to oxygen therapy, including chronic respiratory diseases such as chronic obstructive pulmonary disease. In the oxygen therapy group, potential advantages and risks of oxygen therapy were discussed thoroughly with the patients.

All patients had received ocular irrigation with 1 to 2 L lactated Ringer solution after the injury. Conventional medical therapy included topical antibiotics, steroids, cycloplegics, lubricating ointments, artificial tears, vitamin C 500 mg every 6 hours, and systemic tetracycline 250 mg every 6 hours tapered over 2 to 3 months according to the degree of ocular surface inflammation. All patients were recommended forcefully to perform eyelid blinking, manually to separate the eyelids from the globe, and frequently to perform ductions and versions to decrease the risk of symblepharon formation. Irrigation of the ocular surface with balanced salt solution was performed 4 times daily to reduce ocular surface inflammation. Fibrinous bands and membranes in the upper and lower fornices were removed by gentle movement of the end of a thermometer at each follow-up visit. Patients in the oxygen therapy group were examined by a pulmonologist (E.I.) to rule out any contraindication to oxygen therapy. The main outcome measures were improvement of ischemia and healing of corneal epithelial defects; secondary outcome measures included corneal transparency and vascularization, improvement of visual acuity, and complications.

Corneal transparency and vascularization were graded subjectively and independently from 1+ to 4+ by two examiners (F.S. and M.Z.) 3 and 6 months after surgery. If the cornea was severely opacified and iris details were not visible, it was graded as 1+. If the cornea was clear and iris details were clearly identifiable, transparency was graded as 4+. If there was only 1 vascularized quadrant, vascularization was graded as 1+. If all 4 corneal quadrants were vascularized, it was graded as 4+. For greater accuracy, both slit-lamp findings and digital corneal photographs were used for grading. Mean gradings by the two examiners were considered as the final grade.

Patients were visited daily during the first week, every other day during the second week, and twice weekly thereafter until complete healing. At each follow-up visit, a complete eye examination was performed with special attention to perilimbal ischemia and the extent of corneal and conjunctival epithelial defects. Photographic documentation of slit-lamp findings was performed once or twice weekly.

RESULTS

TWENTY-FOUR EYES OF 22 PATIENTS (ALL MALE) WERE INcluded. Twenty eyes had chemical burns (14 alkaline and 6 acidic) and 4 had thermal burns. Thirteen eyes were included for oxygen therapy and 11 eyes served as controls. Mean age was 27.58 ± 14.29 years (range, 6 to 49 years) in the oxygen therapy and 30.3 ± 10.3 years (range, 19 to 49 years) in the control group ($P = .510$). Mean follow-up period was 18.0 ± 9.27 months (range, 6 to 42 months) in the oxygen group and 18.36 ± 8.33 months (range, 7 to 37 months) in the control group ($P = .734$). Oxygen therapy was initiated at a mean of 9.15 ± 6.91 days (range, 2 to 21 days) after injury. Corneal epithelial defects healed within 15.23 ± 3.94 days (range, 10 to 21 days) after oxygen therapy versus 59.91 ± 23.33 days (range, 28 to 95 days) in the control group (95% confidence interval of the difference, −58.27 to −31.09 days; $P < .001$). Vascularization of ischemic regions began 4 days after oxygen therapy. Vascularization was complete after 14.54 ± 2.70 days (range, 10 to 21 days) in the oxygen therapy group versus 45.09 ± 22.20 days (range, 25 to 105 days) in the control group (95% confidence interval of the difference, −43.38 to −17.73; $P = .001$). Three and 6 months after the injury, corneal transparency was 2.8^+ versus 1.4^+ and 2.6^+ versus 1.3^+ in the oxygen therapy and control groups, respectively. Corresponding values for corneal vascularization were 2.0^+ versus 3.4^+ and 2.0^+ versus 3.2^+ in the oxygen therapy and control groups, respectively. At the end of follow-up, mean visual acuity (logarithm of the minimal angle of resolution) was 0.40 ± 0.52 (0 to 1.3) versus 1.11 ± 0.83 (0.1 ± 3) in the oxygen therapy and control groups ($P = .018$). In the oxygen group, 9 of 13 eyes (0.69%) had useful vision (>20/200) without need for surgery; this situation occurred in 4 (0.36%) of 11 eyes in the control group.

At final follow-up, in the oxygen therapy group, 3 (23%) of 13 eyes had corneal vascularization. Complete vascularization of the cornea developed in 2 eyes (grade IV burns), and in 1 eye (grade III burn), vascularization involved 1 quadrant. Oxygen therapy had been started during the third week after injury in all 3 of these cases. In the control group, complete corneal vascularization developed in all eyes with grade IV burns. In at least 1 quadrant of each eye

TABLE. Characteristics of Patients with Acute Ocular Chemical or Thermal Burns Receiving Oxygen Therapy in Addition to Conventional Medical Therapy

Patient No.	Age (yrs)	Eye	Chemical Agent	Grade of Burn[a]	Beginning of Oxygen Therapy[b]	Epithelial Healing[c]	Improvement of Ischemia[c]	Follow-up (mos)	Final Snellen BCVA (logMAR)
1	16	Right	Alkali	IV	4	14	14	42	20/30 (0.18)
2	6	Right	Thermal	III	20	10	10	30	20/20 (0)
3	13	Left	Thermal	IV	21	21	21	18	20/400 (1.3)
4	40	Right	Alkali	IV	6	16	16	24	20/25 (0.1)
5	44	Right	Acid	III	8	14	14	12	20/25 (0.1)
6	15	Left	Thermal	IV	21	20	15	6	20/400 (1.3)
7	32	Right	Alkali	IV	4	17	17	10	20/25 (0.1)
8	21	Right	Alkali	IV	7	12	14	12	20/30 (0.18)
9	38	Right	Acid	III	3	10	12	16	20/20 (0)
10	18	Right	Thermal	III	5	10	12	12	20/25 (0.1)
11	39	Right	Alkali	III	9	18	14	14	20/40 (0.3)
		Left		III		20	16		20/400 (1.3)
12	49	Left	Alkali	IV	2	16	14	12	20/30 (0.18)

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution; yrs = years.
[a]Based on Roper-Hall classification.
[b]Number of days after injury.
[c]Number of days after oxygen therapy.

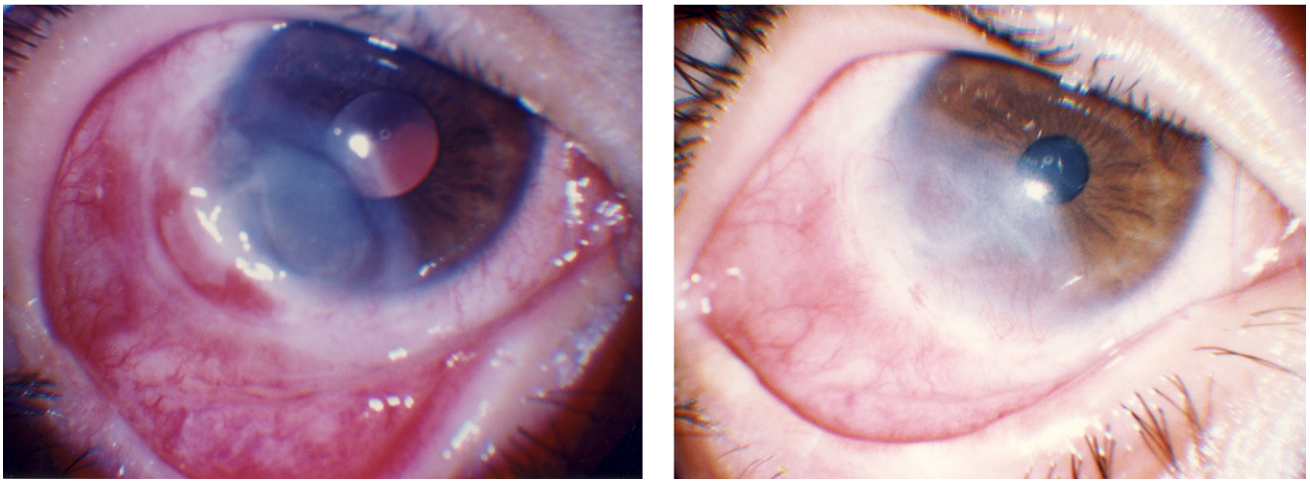

FIGURE. Photographs showing the right eye of Patient 2 with thermal burn. The eye is shown (Left) with corneoscleral melting 20 days after injury while receiving conventional therapy and (Right) with complete healing of the cornea 10 days after oxygen therapy.

with grade III burns, corneal vascularization developed. In 3 eyes with grade IV burns in the control group, symblepharon developed in at least 1 quadrant. Symblepharon and corneal thinning did not occur in any eye in the oxygen group. One patient in the oxygen therapy group (Patient 2), in whom corneoscleral thinning or melting previously had developed before oxygen therapy, regained near-normal corneal thickness within 10 days after oxygen therapy. In the control group, corneoscleral thinning developed in one patient that was corrected with tenoplasty and amniotic membrane transplantation. Patient characteristics in the oxygen therapy group are summarized in the Table.

• **CASE REPORTS:** *Patient 1.* A 16-year-old worker with unilateral ammonia injury in his right eye was referred 4 days after injury. Initial examination revealed visual acuity of hand movements, 360-degree limbal ischemia, large bulbar and palpebral conjunctival epithelial defects, and total corneal epithelial defect with severe edema. A gray inflammatory membrane covered the entire ocular surface with multiple fibrinous bands. One day after oxygen

therapy, corneal edema decreased significantly, allowing detection of severe anterior chamber reaction with heavy pigment dispersion and a dense anterior subcapsular cataract, indicating intraocular penetration of the chemical agent. Four days after oxygen therapy, the gray membrane totally disappeared, small vessels began to grow in the inferonasal and inferotemporal quadrants, and early healing of the corneal epithelium was evident. Progressive vascularization of ischemic areas and healing of the corneal epithelium occurred. Fourteen days later, epithelial defects healed with significant vascularization in most parts of the ischemic conjunctiva. Six months later, the eye was quiet, the cornea was opaque with minimal vascularization, and there was no symblepharon formation. Penetrating keratoplasty together with cataract extraction and intraocular lens implantation was performed 2 years after injury. Final best-corrected visual acuity (BCVA) was 20/30.

Patient 2. A 6-year-old boy with a grade III unilateral thermal burn in his right eye was referred 20 days after injury (Figure). According to his physician, refractory and progressive corneoscleral thinning or melting started 10 days after the burn. BCVA was 20/80 in his right eye. Corneal thickness had decreased to less than one third. Four days after oxygen therapy, small vessels began to grow into the ischemic area. Ten days later, complete healing with fibrovascular tissue replacement occurred and the cornea regained near normal thickness (Figure). Final BCVA was 20/20.

Patient 3. A 13-year-old boy with grade IV thermal burn in his left eye was referred 21 days after injury. Visual acuity was 20/400 and slit-lamp examination revealed 360-degree limbal ischemia, total corneal epithelial defect, and a large conjunctival epithelial defect over the ischemic area. Four days after oxygen therapy, superficial and deep vascularization of the temporal area could be seen with a wave of branching vessels growing toward the limbus leading to conjunctivalization of the cornea. Twenty-one days after oxygen therapy, perilimbal ischemic areas were vascularized completely. Final BCVA was 20/400.

DISCUSSION

OXYGEN THERAPY HAS BEEN USED IN MEDICINE FOR MANY years.[11] Hyperbaric oxygen therapy (HBOT), "the intermittent administration of 100% oxygen at a pressure greater than sea level," has been used to assist wound healing for approximately 50 years.[11] It also has been used for treatment of thermal burns.[12] However, there are only a few reports regarding its use in ophthalmology.[13–15] The current study demonstrated that oxygen therapy may improve perilimbal conjunctival ischemia and may promote corneal epithelial healing in the acute stage of ocular chemical and thermal burns. Such therapy may improve final visual outcomes and long-term prognosis by decreasing corneal conjunctivalization and preventing adnexal complications such as symblepharon formation. Although a controlled study in rabbits showed no beneficial effect from HBOT for corneal alkali burns,[16] another comparative animal model of corneal alkali burns demonstrated beneficial effects from normobaric oxygen therapy (5 L/minute).[17]

It is known that oxygen is capable of favorably influencing a number of cytokines and growth factors that play an important role in wound healing.[11] The effects of transforming growth factor-β 1 and platelet-derived growth factor-β are synergistically enhanced by oxygen. When administered after wounding, oxygen may upregulate collagen synthesis. In ischemic flaps, oxygen can upregulate fibroblast growth factor, increasing the effect observed with fibroblast growth factor alone.[11,18,19] However, oxygen surprisingly may cause upregulation or downregulation of cytokines under different physiological conditions. For example, vascular endothelial growth factor is upregulated by both hypoxia and hyperoxia.[11,20] It is unclear how oxygen is able to stimulate biological processes such as angiogenesis, collagen synthesis, and release of vascular endothelial growth factor at both hypoxic and hyperoxic concentrations, a phenomenon referred to as the *oxygen paradox*.

Tissue oxygen level plays a major role in the physiology of blood flow, wound healing, and white cell function. The beneficial effects of oxygen primarily are related to its concentration within tissues.[21] Low tissue oxygen pressure (5 to 15 mm Hg) diminishes the ability of white blood cells to kill bacteria and decreases collagen synthesis by fibroblasts. Raising tissue oxygen tensions to 30 to 40 mm Hg provides the substrate necessary to lay down a collagen matrix for support of capillary ingrowth into avascular or damaged areas.[21] Although oxygenation of hypoxic tissue is a key mechanism in accelerating wound healing, oxygen also acts in numerous ways that affect the wound after termination of treatment. Oxygen benefits wounds by several mechanisms, including upregulation of growth factors, downregulation of inflammatory cytokines, reduction of edema, and improvement in leukocyte function. Furthermore, it demonstrates antibacterial effects and at the same time supports angiogenesis and new tissue ingrowth.[11,20,21]

The main objectives of management for acute chemical or thermal burns are reduction of limbal stem cell loss and acceleration of corneal and conjunctival epithelialization with or without vascularization. Limbal ischemia, which may reflect the extent and severity of limbal stem cell damage, has been suggested as the most important prognostic factor in ocular chemical or thermal injuries.[4] Destruction of limbal stem cells may be progressive in the first few days after injury. By reducing ischemia, oxygen may decrease the extent of progressive stem cell damage and improve prognosis. However, this effect may be

observed only if treatment is initiated early after injury. Earlier epithelial healing prevents long-term complications associated with persistent epithelial defects, including bacterial superinfections, tissue melting, endophthalmitis, and symblepharon formation. In our study, epithelial healing occurred much earlier in the oxygen-treated group as compared with those receiving conventional therapy.

The sensitivity of different cell types to ischemia varies greatly. Before sustaining irreversible damage, neurons tolerate ischemia for 4 to 10 minutes,[22] whereas the corresponding time for myocardial cells is 20 minutes.[23] It is thought that at least 25% to 33% of the limbal stem cell population is required to maintain corneal epithelial integrity.[24] With acute or prolonged ischemia, some cells die, whereas others are viable but dysfunctioning.[22] Salvage of as many dysfunctioning cells as possible may affect the outcome of any insult favorably. Early oxygen therapy may save partially injured ischemic limbal and conjunctival stem cells, may promote corneal and conjunctival epithelialization, may prevent corneal conjunctivalization, may trigger scleral vascularization, and may prevent its melting or perforation. Therefore, the cornea may become covered by a transparent layer of epithelium. With late intervention, despite complete destruction of limbal and conjunctival stem cells and their niche, oxygen therapy still may be effective in inducing angiogenesis and promoting corneal vascularization. Tissue vascularization may appear as heavy tufts of vessels entering the remodeling phase in the following few days. In this situation, the cornea may be covered by conjunctival epithelium. Interestingly, in some eyes receiving oxygen therapy, we observed the wave of healing corneal epithelium to precede healing conjunctival epithelium, indicating separate sources of corneal and conjunctival epithelial healing.

Reducing inflammation may hinder limbal stem cell destruction and may promote corneal and conjunctival epithelialization. The role of intense and prolonged topical steroids and topical and systemic vitamin C in decreasing ocular surface inflammation after chemical burns already has been demonsterated.[25] Amniotic membrane transplantation also has been shown to reduce inflammation and to promote epithelialization in the acute phase of chemical and thermal injuries with conflicting results.[9,26,27] It has been shown that oxygen plays a role in decreasing inflammation by downregulating inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor.[11]

Simple mask oxygen therapy is a low-flow oxygen delivery system that differs from HBOT in many aspects. It increases arterial blood oxygen pressure (PaO_2) from a baseline of approximately 95 mm Hg to levels up to 250 mm Hg, whereas HBOT can increase it up to 1700 mm Hg at 2.4 atmospheric pressure.[12] HBOT is contraindicated in pregnancy, otitis media, congestive heart failure, pneumothorax, and chronic obstructive pulmonary disease,[11] whereas simple mask oxygen therapy can be used safely in these situations. However, in patients with chronic obstructive pulmonary disease and hypercarbia (carbon dioxide pressure $>$ 45 mm Hg), simple mask oxygen therapy must be used cautiously.[28] The most common complications of HBOT, but not simple mask oxygen therapy, are ear and sinus barotrauma, myopia, oxygen seizures, and pulmonary barotrauma.[11]

There are some limitations to our study. This study was an interventional, nonrandomized, comparative case series with a limited number of cases. Although some beneficial effects of oxygen therapy were well demonstrated, our study was inconclusive about the optimal starting time and frequency and flow rate for oxygen therapy. However, it reasonably may be argued that oxygen therapy should be started as soon as possible after chemical or thermal burns.

In summary, oxygen therapy seems to be safe and effective in ameliorating some of the devastating complications of acute ocular chemical and thermal burns. This method is readily available at all hospital facilities, is inexpensive, and is noninvasive. We recommend it be integrated into the early routine management for acute ocular chemical and thermal burns. Further studies are warranted to confirm our observations; to determine the pathophysiologic mechanisms; to establish the optimal therapeutic regimen, including frequency, flow rate, and time for initiating oxygen therapy; and to elucidate better the benefits and drawbacks to oxygen therapy.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICTS OF INTEREST. INVOLVED IN DESIGN OF STUDY (F.S., A.B.R., E.I.); Conduct of study (F.S., A.B.R., E.I., M.Z., M.J.); Collection (F.S., A.B.R., M.Z., M.J.), management (F.S., A.B.R., E.I., M.Z.), and Analysis and interpretation (F.S., E.I., M.J.) of data; and Preparation and review of the manuscript (F.S., A.B.R., E.I., M.Z., M.J.). This study was approved by the Institutional Review Boards and Ethics Committees of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, and Shahid Beheshti University of Medical Sciences, Tehran, Iran. Informed consent was obtained from all patients for both treatment and participation in the study. The study adheres to the tenets of the Declaration of Helsinki.

REFERENCES

1. Pfister RR, Pfister DR. Alkali injuries of the eye. In: Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea. 2nd ed. Philadelphia: Elsevier Mosby, 2005:1285–1293.
2. Sutphin JE, Dana MR, Florakis GJ, eds. Basic and Clinical Science Course: External Diseases and Cornea. San Francisco: American Academy of Ophthalmology, 2008–2009:389–393.
3. Ralph RA. Chemical injuries of the eye. In: Tasman W, Jaeger EA, eds. Duane's Ophthalmology on CD-ROM. Vol. 4, chap. 28. Philadelphia: Lippincott Williams & Wilkins, 2009.

4. Wagoner MD. Chemical injuries of the eye: current concepts in pathophysiology and therapy. Surv Ophthalmol 1997; 41(4):275–313.
5. Levinson RA, Paterson CA, Pfister RR. Ascorbic acid prevents corneal ulceration and perforation following experimental alkali burns. Invest Ophthalmol Vis Sci 1976; 15(12):986–993.
6. Pfister RR, Haddox JL, Lank KM. Citrate or ascorbate/citrate treatment of established corneal ulcers in the alkali-injured rabbit eye. Invest Ophthalmol Vis Sci 1988;29(7):1110–1115.
7. Seedor JA, Perry HD, McNamara TF, Golub LM, Buxton DF, Guthrie DS. Systemic tetracycline treatment of alkali-induced corneal ulceration in rabbits. Arch Ophthalmol 1987;105(2):268–271.
8. Kenyon KR, Berman M, Rose J, Gage J. Prevention of stromal ulceration in the alkali-burned rabbit cornea by glued-on contact lens. Evidence for the role of polymorphonuclear leukocytes in collagen degradation. Invest Ophthalmol Vis Sci 1979;18(6):570–587.
9. Meller D, Pires RT, Mack RJ, et al. Amniotic membrane transplantation for acute chemical or thermal burns. Ophthalmology 2000;107(5):980–989.
10. Roper-Hall MJ. Thermal and chemical burns. Trans Ophthalmol Soc UK 1965;85:631–653.
11. Wright J. Hyperbaric oxygen therapy for wound healing. Available at: http://www.worldwidewounds.com/2001/april/wright/Hyperbaricoxygen.html. Accessed May 2001.
12. Moon RE, Camporesi EM. Clinical care in extreme environments: at high and low pressure and in space. In: Miller RD, eds. Miller's Anesthesia. 7th ed. Philadelphia: Churchill Livingstone/Elsevier, 2010:2485–2515.
13. Oguz H, Sobaci G. The use of hyperbaric oxygen therapy in ophthalmology. Surv Ophthalmol 2008;53(2):112–120.
14. Green MO, Brannen AL. Hyperbaric oxygen therapy for beta-radiation-induced scleral necrosis. Ophthalmology 1995; 102(7):1038–1041.
15. Bayer A, Mutiu FM, Sobaci G. Hyperbaric oxygen therapy for mitomycin C-induced scleral necrosis. Ophthalmic Surg Lasers 2001;32(6):490–493.
16. Hirst LW, Summers PM, Griffiths D, Bancroft J, Lillicrap GR. Controlled trial of hyperbaric oxygen treatment for alkali corneal burn in the rabbit. Clin Experiment Ophthalmol 2004;32(1):67–70.
17. Sharifipour F, Zamani M, Idani E, Hemmati AA. Oxygen therapy for severe corneal alkali burn in rabbits. Cornea 2007;26(9):1107–1110.
18. Wu L, Mustoe TA. Effect of ischemia on growth factor enhancement of incisional wound healing. Surgery 1995; 117(5):570–576.
19. Mustoe TA, Tae Ahn S, Tarpley JE, Pierce GF. Role of hypoxia in growth factor responses: differential effects of basic fibroblast growth factor and platelet-derived growth factor in an ischemic wound model. Wound Repair Regen 1994;2(4):277–283.
20. Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z, Hunt TK. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. Arch Surg 2000;135(11): 1293–1297.
21. Bordow RA, Ries AL, Morris TA, eds. Manual of Clinical Problems in Pulmonary Medicine. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2005:102–108.
22. Smith WS, English JD, Johnston SC. Cerebrovascular diseases In: Fauci AS, Braunwald E, Kasper DL, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill, 2008:2513–2536.
23. Antman EM, Selwyn AP, Braunwald E, Loscalzo J. Ischemic heart disease. In: Fauci AS, Braunwald E, Kasper DL, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill, 2008:1514–1527.
24. Sutphin JE, Dana MR, Florakis GJ, eds. Basic and Clinical Science Course: External Diseases and Cornea. San Francisco: American Academy of Ophthalmology, 2008–2009: 108.
25. Davis AR, Ali QK, Aclimandos WA, Hunter PA. Topical steroid use in the treatment of ocular alkali burns. Br J Ophthalmol 1997;81(9):732–734.
26. Joseph A, Dua HS, King AJ. Failure of amniotic membrane transplantation in the treatment of acute ocular burns. Br J Ophthalmol 2001;85(9):1065–1069.
27. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology 2005;112(11):1963–1969.
28. Reilly JJ, Silverman EK, Shapiro SD. Chronic obstructive pulmonary disease. In: Fauci AS, Braunwald E, Kasper DL, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill, 2008:1635–1643.