
Low-level laser therapy for diabetic foot wound healing.(Wound care)

Source: The Diabetic Foot

Date: 12/22/2005

Author: Houreld, Nicolette;Abrahamse, Heidi

Introduction

An alternative to traditional treatment modalities for diabetic ulcers is low-level laser therapy (LLLT). A number of published studies demonstrate the beneficial effects of LLLT (Ribeiro et al, 2002), although several other studies also exist which indicate results to the contrary (Malm and Lundeborg, 1991; Loevschall and Arenholt-Bindslev, 1994). Further work focusing on cellular and molecular mechanisms of responses to laser irradiation is required to establish LLLT as a reliable, safe and inexpensive treatment modality. This article reviews LLLT as a treatment modality for diabetic ulcers.

KEY WORDS

* Wound healing

* Laser therapy

* Photobiostimulation

Due to its serious complications diabetes remains an important cause of morbidity and mortality. The principal complications arise from macro- and microangiopathy. The nervous system is also affected, which can lead to sensory loss and subsequent damage to the limbs. Atrophy of fat and muscle tissue, combined with sensory loss, can result in pressure sores on the feet, which, in turn, can lead to lower-limb amputation. Approximately 15% of people with diabetes will develop

foot ulcers, and 6% of these will require hospitalization for the treatment of such ulcers (Carrington et al, 2001). Diabetes accounts for 50% of all non-traumatic amputations (Schindl et al, 1998). Changes to the vascular system results in delayed wound healing. People with diabetes have poor circulation, poor resistance to infection, and poor local nutrition, thus these wounds are highly susceptible to infection.

Low-level laser therapy

Low-level laser therapy (LLLT; also known as biostimulation and photobiostimulation) is a form of phototherapy that involves the application of low-power monochromatic and coherent light to injuries and lesions in order to stimulate wound healing. LLLT has been shown to increase the speed, quality and tensile strength of tissue repair, resolve inflammation and provide pain relief (supporting literature is reviewed later in the article). Lasers are already used in a variety of medical and surgical fields, including dentistry, chiropractice, osteopathy, physiotherapy, cosmetic, pain attenuation, wound healing and acupuncture to name but a few (e.g. Walsh, 1997).

The effects of LLLT are photochemical, not thermal, and the responses of cells occur due to changes in photoacceptor molecules (also known as chromophores [molecules which are able to absorb photonic energy]; Tuner and Hode, 2002), such as porphyrin. The exact mechanism of action of LLLT is not completely understood. However, it is known that during laser irradiation cells absorb photonic energy that is incorporated into chromophores, which, in turn, stimulates cellular metabolism (Pineiro et al, 2002).

The chromophore is able to transfer the absorbed energy to other molecules and thus cause chemical reactions in surrounding tissue. The acceptor molecules' kinetic energy is increased, thereby activating or deactivating enzymes, which, in turn, are able to alter the physical and/or chemical properties of other macromolecules (for example DNA and RNA; Matic et al, 2003; Takac and Stojanovic, 1998) in order to facilitate wound healing. Energy which is delivered to the cells produces insignificant and minimal temperature changes, typically in the range of 0.1-0.5[degrees]C (Nemeth, 1993).

LLLT and wound healing

Normal wound healing requires both destructive and reparative processes in controlled balance. Proteases and growth factors play an important role in regulating this balance, and if disrupted in favour of degradation then delayed healing ensues, which is a trait of chronic wounds (Cullen et

al, 2002). It has been shown that low-level laser irradiation at certain fluences and wavelengths can enhance the release of growth factors and stimulate cell proliferation (Yu et al, 2001).

The effects of LLLT include wound epithelialisation, reduction of oedema and inflammation, and re-establishment of arterial, venous and lymph microcirculation. Increased rates of ATP, RNA and DNA synthesis are also observed (Takac and Stojanovic, 1998). Major changes seen in wounds treated with LLLT include increased granulation tissue, early epithelialisation, increased fibroblast proliferation, increased extracellular matrix synthesis and enhanced neovascularisation (Walsh, 1997), all of which lead to better tissue oxygenation and nutrition, and, in turn, enhanced wound healing. The effects of LLLT on wound healing are summarised in Table 1.

It has been shown that low-level irradiation of fibroblasts stimulates the production of basic fibroblast growth factor and stimulates the transformation of fibroblasts into myofibroblasts (Walsh, 1997). LLLT also affects immune cells, and acts directly and selectively on the immune system (Tadakuma, 1993). Stimulation of the immune system means that infected wounds can be cleared more readily. The use of low-level lasers in wound healing has been shown to speed up the healing of leg ulcers and burn wounds; it has also been shown to improve skin-healing capabilities (Ribeiro et al, 2002).

LLLT and wound healing in vitro

It has been shown that exposure to a 308nm excimer laser reduces bacterial growth in vitro (Folwaczny et al, 1998). This may be of significant clinical importance in bacterially infected wounds: not only could LLLT increase wound closure, but it may also speed up the clearing of an infected wound--a definite benefit to people with diabetes.

LLLT and diabetic wound healing in rodents

Yu and colleagues (1997) evaluated whether low-level laser irradiation could improve wound healing in mice with diabetes. Genetically diabetic mice (C57BL/KsJ-db/db) were exposed to an argon dye laser (wavelength: 630nm; power density: 20mW/[cm.sup.2] [see Table 2 for definitions]). They demonstrated that laser irradiation enhanced wound closure over time; histological evaluation indicated improved wound epithelialisation, cellular content, granulation tissue formation and collagen deposition as compared to the negative control group.

LLLT has also been shown to enhance cutaneous wound tensile strength. Stadler and colleagues (2001) exposed the wounds of wounded female C57BL/KsJ-db/db mice to low-level laser

irradiation and measured tensile strength. The wounded mice were exposed to low-level laser irradiation daily for 5 days, (wavelength: 830nm; power density: 79mW/[cm.sup.2]; energy density: 5.0J/[cm.sup.2] [see Table 2 for definitions]) starting either on the day of wounding or 3 days later. Compared with control mice (which received no irradiation) there was an increase in tensile strength in exposed mice sacrificed on days 11 and 23 post-injury. Higher tensile strengths were noted at 23 days in mice that received their course of irradiation 3 days after wounding. Stadler and colleagues (2001) felt that further investigation of the mechanism of LLLT in primary wound healing is warranted.

Reddy and colleagues (2001) concluded that photobiostimulation promotes tissue repair by accelerating the production of collagen and promotes overall connective tissue stability in wound healing. Male rats with streptozotocin-induced diabetes received circular wounds 6mm in diameter either side of the spine--one wound was treated with a helium--neon (He--Ne) laser (wavelength: 632.8nm; energy density: 1.0J/[cm.sup.2]) 5 days per week until there was wound closure. The other wound received no laser irradiations and was used as the control. In 2003, Reddy compared these results with wounded rats with streptozotocin-induced diabetes exposed to a gallium--arsenide (Ga--As) laser (wavelength: 904nm; energy density: 1.0J/[cm.sup.2]). The wound to the left of the spine was irradiated 5 days per week for a period of 3 weeks, while the wound to the right was used as a control. After 3 weeks, the rats were sacrificed and the wound sites analysed (Reddy, 2003). Measurements of the He--Ne-irradiated wounds indicated there was an increase in maximum load, stress, strain, energy absorption and toughness compared with the controls (Reddy et al, 2001). There was an increase in tensile strength and toughness of the wound exposed to the Ga--As laser as compared with the control wounds. There were no changes in energy absorption between the control and irradiated wounds (Reddy, 2003).

Biochemical analysis revealed that the amount of total collagen was significantly increased in laser-treated wounds over control wounds, with an increase in the concentration of acid- and salt-soluble collagen and insoluble collagen. There was also a decrease in proteolytic digestion as measured by a decrease in pepsin-soluble collagen (Reddy et al, 2001; Reddy, 2003). It is the opinion of Reddy (2003) that irradiation with an He--Ne laser for wound healing in mice with diabetes is better than irradiation with a Ga--As laser, and that the different biochemical responses may be wavelength and coherence dependent.

LLLT and diabetic wound healing in humans

Exposure to low-level laser irradiation abates the inflammatory reaction and stimulates the

immune system, leading to an increase in wound healing in infected wounds in people with diabetes (Khurshudian, 1989). Khurshudian treated 174 people with diabetes with suppurative diseases. Patients were exposed to a helium--cadmium laser beam of wavelength 441.6nm. A single exposure to 4.5J/[cm.sup.2] led to a rapid decrease in the inflammatory reaction, and there was a cleansing and acceleration of regeneration processes in the infected wounds.

This was supported by work conducted by Kuliev and Babaev (1991). They studied the immune status after laser irradiation in 152 people with diabetes with purulent soft tissue injuries. There was a rapid stabilisation of the immune system, thus reducing the duration of treatment. Potinen (1992) determined the stabilisation of the immune system by the observation of the increased release of various cytokines upon LLLT. He also observed an increase in the leucocyte population and an arrest in bacterial growth.

Kuliev and colleagues (1992) determined the effectiveness of including both a magnetic field (provided by various methods such as magnetic bracelets and wraps) and LLLT in the treatment of 119 people with diabetes with suppurative wounds. Immunological status was stabilised in a shorter time and the process of wound healing followed a quicker course, resulting in a shortened treatment time. It was suggested that the magnetic-laser combined effect has an advantage over the separate use of these factors.

Low-level laser irradiation induces wound healing in conditions of reduced microcirculation. Schindl and colleagues investigated the effect of LLLT in patients with diabetic microangiopathy by infrared thermography on skin blood circulation (Schindl et al, 1998; Schindl et al, 2002). In the first study (Schindl et al, 1998), 30 people with diabetic ulcers or gangrene received either a single low-intensity laser irradiation (He--Ne laser; wavelength: 632.8nm; beam power: 30mW; energy density: 30J/[cm.sup.2]), or a sham irradiation over both forefoot regions. At 20 minutes of laser irradiation, there was a significant rise in skin temperature in the forefoot area, with an increase of 0.58 [+ or -] 0.68[degrees]C (P<0.001). The increase was 1.06 [+ or -] 1.03[degrees]C at the end of irradiation (50 minutes; P<0.001) and 1.22 [+ or -] 1.01[degrees]C (P<0.001) 15 minutes after the end of irradiation. There was a slight, but significant, drop in skin temperature in the placebo group (P<0.001).

In the second study (Schindl et al, 2002), patients were exposed once to an He--Ne laser, (wavelength: 632.8nm; energy density: 30J/[cm.sup.2]), or a sham irradiation over the forefoot region of one foot. A rise in skin temperature in both feet in the laser group was noted, whereas a drop in both feet in the placebo group was noted. The group showed that athermic laser

irradiation on one foot in people with diabetes with angiopathy causes a significant increase in skin circulation in both feet and points to the possibility of systemic effects.

Schindl and colleagues (Schindl et al, 1999) conducted a study on a person with diabetes with sensory neuropathy, macroangiopathy and microangiopathy. The patient was exposed (in 16 sessions within a 4-week period) to a 670nm diode laser, as well as conventional treatments (such as using dressings and antibiotics). There was complete healing of the ulcer with no recurrence after 9 months, despite the patient's unstable metabolic condition. Despite the fact that LLLT was not applied alone, LLLT may be a useful alternative treatment modality for the induction of wound healing of ulcers in people with diabetes which is free of side effects.

Exposure of blood to LLLT results in a decrease in free radical oxidation (Grigor'eva et al, 1991). Grigor'eva and colleagues investigated the activity of primary and secondary products of lipid peroxidation and antiperoxide protection enzymes. The blood of 33 people with diabetes was irradiated for 60 minutes with the help of a light guide. After laser irradiation, there was a decrease in the activity of processes of free radical oxidation compared with blood samples taken before laser irradiations. This decrease is probably due to the effect of LLLT on antiperoxide enzymes. The group also found an increase in microcirculation, which is in accordance with the work of Schindl and colleagues (Schindl et al, 1998; 2002).

Current literature

Currently there is no accepted theory to explain the mechanism of low-level laser biostimulation, and this lack of knowledge complicates the evaluation of conflicting reports in the literature. Lasers have been shown to be both stimulatory and inhibitory. These differences in the literature can be explained by the different treatment parameters used, such as wavelength, fluence, output power and treatment regimens (Baxter et al, 1991). Few articles provide all the relevant laser parameters, making it difficult to reproduce the work. Patient status, size and type of wound also play important roles. LLLT has been used extensively in former Eastern bloc countries, thus there is a vast amount of experience and information available, although most of this work is published in Russian journals, and during the translation of these papers information can become lost.

According to the American Diabetes Association (1999), the following criteria should be included when evaluating new treatments for diabetic foot wound care: randomised controlled studies; a sufficient number of patients; relevant outcomes; control patients; primary end point, with a proportion of patients with complete wound healing within the study period; and evaluation of the

cost and effectiveness of the treatment and the quality of the patient's life. Of all the studies mentioned in this paper, none of them make mention of the costs and quality of patient life. The paper by Schindl and colleagues (1999) was written on a single patient.

Conclusion

The exploitation of phototherapy in medicine and surgery is of great interest, and there is a growing interest in the use of lasers for the treatment of various conditions and disorders, including the treatment of diabetic wounds. There is a need to develop alternative treatment modalities which can improve the endogenous capacity of the healing process, particularly during disease conditions with impaired wound healing. Using lasers as a source of photobiostimulation looks to be an attractive branch of medicine for the future.

Chronic skin ulcers present a challenge in dermatology, and among the various non-invasive treatments used in wound healing, LLLT has steadily increased in its applications to include a wide variety of medical and surgical specialties (such as physiotherapists, dentists, dermatologists and rheumatologists, and also in nerve regeneration; Karu, 2003). LLLT as a treatment is a choice that appeals to people (Forney and Mauro, 1999), it is a simple and non-invasive treatment that offers pain relief and has no reported side effects. As outlined above, LLLT has been shown by various studies to be effective in the treatment of diabetic wound healing.

Due to disturbances of the circulation in people with diabetes, wounds heal slowly and are susceptible to infection. LLLT has been shown to speed up the time needed for wound closure in people with diabetes (Khurshudian, 1989; Kuliev and Babaev, 1991; Yu et al, 1997; Reddy et al, 2001); and there is improved wound epithelialisation, increased cellular content, increased granulation tissue formation and increased collagen deposition (Yu et al, 1997). There is a decrease in the inflammatory reaction (Khurshudian, 1989), and a stimulatory effect on the immune system (Khurshudian, 1989; Kuliev and Babaev, 1991). LLLT has also been shown to increase microcirculation (Grigor'eva et al, 1991; Schindl et al, 1998; Schindl et al, 1999; Schindl et al, 2002), enhance wound tensile strength (Stadler et al, 2001), accelerate collagen production (Reddy et al, 2001; Reddy, 2003), and decrease free radical oxidation processes (Grigor'eva et al, 1991) in people with diabetes.

Due to the increasing cost of care of diabetic wounds, and the burden incurred by the patients and society, there is a need to develop new, inexpensive and safe treatment modalities which

increase wound healing. From the results of published studies on diabetic wound healing, large, properly controlled studies seem justified. At the correct wavelength, intensity and fluence, LLLT can be a complementary therapy modality in the treatment of impaired wound healing and future research should be developed to find adequate wavelengths and doses.

American Diabetes Association (1999) Consensus development conference on diabetic foot wound care. *Diabetes Care* 22(8): 1354-60

Baxter GD, Bell AJ, Allen JM and Ravey J (1991) Low level laser therapy: Current clinical practice in Northern Ireland. *Physiotherapy* 77(3): 171-8

Carrington AL, Abbott CA, Griffiths J, Jackson N, Johnson SR, Kulkarni J et al (2001) A foot care program for diabetic unilateral lower-limb amputees. *Diabetes Care* 24(2): 216-21

Cullen B, Watt PW, Lundqvist C, Silcock D, Schmidt RJ, Bogan D, Light ND (2002) The role of oxidised regenerated cellulose/collagen in chronic wound repair and its potential mechanism of action. *The International Journal of Biochemistry and Cell Biology* 34(12): 1544-56

Folwaczny M, Liesenhoff T, Lehn N, Horch HH (1998) Bactericidal action of 308 nm excimer-laser radiation: an in vitro investigation. *Journal of Endodontics* 24(12): 781-5

Forney R, Mauro T (1999) Using lasers in diabetic wound healing. *Diabetes Technology and Therapeutics* 1(2): 189-92

Grigor'eva IV, Rakita DR, Garmash V Ia (1991) [Effect of endovascular laser irradiation of the blood of patients with diabetic angiopathies.] *Problemy Endokrinologii (Mosk)* 37(6): 28-30

Karu TI (2003) Low level laser therapy. In: T Vo-Dinh ed. *Biomedical photonics handbook*. CRC Press, Florida, USA, chapter 48: 1-25

Khurshudian AG (1989) [Use of helium-cadmium lasers in the complex treatment of suppurative diseases in patients with diabetes mellitus.] *Khirurgiia (Mosk)* June(6): 38-42

Kuliev RA, Babaev RF (1991) [Therapeutic action of laser irradiation and immunomodulators in purulent injuries of the soft tissues in diabetic patients.] *Problemy Endokrinologii (Mosk)* 37(6): 31-2

Kuliev RA, Babaev RF, Akhmedova LM, Ragimova AI (1992) Treatment of suppurative wounds in

patients with diabetes mellitus by magnetic field and laser irradiation. *Khirurgiia (Mosk)* July-August(7-8): 30-3

Loevschall H, Arenholt-Bindslev D (1994) Effect of low level diode laser irradiation of human oral mucosa fibroblasts in vitro. *Lasers in Surgery and Medicine* 14(4): 347-54

Malm M, Lundeberg T (1991) Effect of low power gallium arsenide laser on healing of venous ulcers. *Scandinavian Journal of Plastic Reconstructive Surgery and Hand Surgery* 25(3): 249-51

Matic M, Lazetic B, Poljacki M, Duran V, Ivkov-Simic M (2003) [Low level laser irradiation and its effect on repair processes in the skin.] *Medicinski Pregled* 56(3-4): 137-41

Nemeth AJ (1993) Lasers and wound healing. *Dermatologic Clinics* 11(4): 783-9

Pearl SH, Kanat IO (1988) Diabetes and healing: a review of the literature. *The Journal of Foot Surgery* 27(3): 268-70

Pinheiro AL, Carneiro NS, Vieira AL, Brugnera A Jr, Zanin FA, Barros RA, Silva PS (2002) Effects of low-level laser therapy on malignant cells: in vitro study. *Journal of Clinical Laser Medicine and Surgery* 20(1): 23-6

Potinen PJ (1992) Biological effects of LLLT. In: PJ Potinen, ed. *Low level laser therapy as a medical treatment modality*. Art Urpo, Tampere, Finland, 99-101

Reddy GK (2003) Comparison of the photostimulatory effects of visible He-Ne and infrared Ga-As lasers on healing impaired diabetic rat wounds. *Lasers in Surgery and Medicine* 33(5): 344-51

Reddy GK, Stehno-Bittel L, Enwemeka CS (2001) Laser photostimulation accelerates wound healing in diabetic rats. *Wound Repair and Regeneration* 9(3): 248-55

Ribeiro MS, Silva DF, Maldonado EP, de Rossi W, Zezell DM (2002) Effects of 1047-nm neodymium laser radiation on skin wound healing. *Journal of Clinical Laser Medicine & Surgery* 20(1): 37-40

Schindl A, Heinze G, Schindl M, Pernerstorfer-Schon H, Schindl L (2002) Systemic effects of low-intensity laser irradiation on skin microcirculation in patients with diabetic microangiopathy. *Microvascular Research* 64(2): 240-6

Schindl A, Schindl M, Pernerstorfer-Schon H, Kerschman K, Knobler R, Schindl L (1999) Diabetic neuropathic foot ulcer: successful treatment by low-intensity laser therapy. *Dermatology* 198(3): 314-6

Schindl A, Schindl M, Schon H, Knobler R, Havelec L, Schindl L (1998) Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. *Diabetes Care* 21(4): 580-4

Stadler I, Lanzafame RJ, Evans R, Narayan V, Dailey B, Buehner N, Naim JO (2001) 830-nm irradiation increases the wound tensile strength in a diabetic murine model. *Lasers in Surgery and Medicine* 28(3): 220-6

Tadakuma T (1993) [Possible application of the laser in immunobiology.] *The Keio Journal of Medicine* 42(4): 180-2

Takac S, Stojanovic S (1998) [Diagnostic and biostimulating lasers.] *Medicinski Pregled* 51(5-6): 245-9

Tuner J, Hode L (2002) *Laser therapy: Clinical practice and scientific background*. Prima Books, Grangesburg, Sweden. 45-114

Walsh LJ (1997) The current status of low level laser therapy in dentistry. Part I. Soft tissue applications. *Australian Dental Journal* 42(4): 247-54

Yu W, Naim JO, Lanzafame RJ (1997) Effects of photostimulation on wound healing in diabetic mice. *Lasers in Surgery and Medicine* 20(1): 56-63

Nicolette Houreld is a Doctoral Student and Professor Heidi Abrahamse a Senior Research Fellow at The Laser Research Unit, Faculty of Health Sciences, Doornfontein, Johannesburg, South Africa.

RELATED ARTICLE: ARTICLE POINTS

1 Low-level laser therapy (LLLT) is an alternative treatment modality for diabetic wounds.

2 LLLT increases the speed, quality and tensile strength of tissue repair, and also resolves inflammation and provides pain relief.

3 LLLT is a noninvasive treatment with no reported side effects.

4 LLLT improves wound epithelialisation and increases cellular content, granulation tissue, collagen deposition and microcirculation.

5 LLLT stimulates the immune system, enhances wound tensile strength and decreases free radical oxidation processes.

RELATED ARTICLE: PAGE POINTS

1 The use of low-level lasers in wound healing has been shown to speed up healing of leg ulcers and burn wounds; it has also been shown to improve skin-healing capabilities.

2 It has been shown that exposure to a 308nm excimer laser reduces bacterial growth in vitro.

RELATED ARTICLE: PAGE POINTS

1 Low-level laser therapy has also been shown to enhance cutaneous wound tensile strength.

2 Irradiation with an He-Ne laser for wound healing in mice with diabetes is better than irradiation with a Ga-As laser, and that the different biochemical responses may be wavelength and coherent dependent.

RELATED ARTICLE: PAGE POINTS

1 The magnetic-laser effect has an advantage over the separate use of these factors.

2 Exposure of blood to LLLT has shown a decrease in free radical oxidation.

3 LLLT as a treatment is a choice that appeals to people, it is a simple and non-invasive treatment that offers pain relief and has no reported side effects.

4 Due to disturbances to circulation in people with diabetes, wounds heal slowly and are susceptible to infection.

RELATED ARTICLE: PAGE POINTS

1 Due to the increasing cost of care of diabetic wounds, and the burden incurred by the patients

and society, there is a need to develop new, inexpensive and safe treatment modalities, which increase wound healing.

Table 1. Summary of events during wound healing and the effects of low-level laser therapy (LLLT; adapted from Pearl and Kanat, 1988).

Phase	Duration	Events
Lag	0-10 days	Inflammation Clot formation Epithelialisation Fibroblast migration
Proliferation	2-4 weeks	Mitogenesis Fibrinogenesis Cellular migration Wound contraction Angiogenesis Granulation tissue
formation		
Remoulding	[greater than or equal to]1 year	Epithelialisation Scar formation Collagen maturation Collagen synthesis and
lysis		in balance
Phase	Effects of LLLT at all phases	
Lag	Increased epithelialisation Re-establishment of arterial venous and lymph microcirculation Decreased oedema Pain attenuation	
Proliferation	Increased ATP, RNA and DNA synthesis Increased granulation tissue Increased mitogenesis Increased neovascularisation Increased matrix synthesis Increased fibrinogenesis Decreased inflammation Increased cytokines and growth factors Increased stimulation of immune system	
Remoulding	Increased tissue nutrition and oxygenation Increased wound closure Increased angiogenesis Increased tensile strength	

Table 2. Explanation of units used for LLLT.

Power density refers to the light output per unit area of the target tissue being irradiated. This is measured in watts per square centimetre

(W/[cm.sup.2]) or milliwatts per square centimetre (mW/[cm.sup.2]).

Energy density is equivalent to dose (or fluence) and is measured in joules per square centimetre (J/[cm.sup.2]). Energy density refers to the amount of energy per unit area brought to bear on the tissue being irradiated. It is measured using the following formula.

Energy density (D;J/[cm.sup.2]) = [power (W; watts) X time (s; seconds)]/[area treated ([cm.sup.2])]

The wavelength of the lasers used is always measured in nanometres (nm).

COPYRIGHT 2005 S.B. Communications

This material is published under license from the publisher through the Gale Group, Farmington Hills, Michigan. All inquiries regarding rights should be directed to the Gale Group.

[Click here to see more articles](#) on this topic.

[Try your research topic on HighBeam Research](#) now (great for any business, educational or personal research need).

About HighBeam™ Research

HighBeam Research, Inc. (formerly Alacritude, LLC) operates an online research engine for individuals, filling the gap between free search engines and high-end research services. By delivering sophisticated research tools with convenient access to the free Web, paid online services, and our proprietary Library database, we empower individual researchers to efficiently locate, organize and deliver answers. HighBeam Research is located at www.highbeam.com.