



Results of the Treatment Vascular Anomalies with the 5 ALA Induced Photodynamic Therapy

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Abstract

This study reports the role of photodynamic therapy in the management of vascular anomalies. A 3-year (2009-2012) retrospective study on the challenges and outcome of two hundred forty five patients with vascular anomalies referred for surgical management was undertaken at the Tashkent Medical Academy, Uzbekistan. After multidisciplinary discussion, all patients underwent photodynamic therapy under general anesthesia, with 5-ALA as the photosensitising agent. In a time of treatment by eighty five out of one hundred and eight patients, who presented with long-term pain, reported improvement after treatment. Also, 43/46 reported significant reduction of bleeding related to their vascular anomaly. Improvement of swelling was reported by 189/199 patients; while reduction of infection episodes was evident in 61/63 patients and 176/205 reported reduction in the disfigurement caused by their pathology. Clinical assessment showed that more than half of the patients had 'good response' to the treatment. Significant clinical response was reported by 148 (60, 4%) patients, moderate result by 70 (28, 6%). Radiological and ultrasound assessment comparing imaging 6-week post-laser and PDT to the baseline showed moderate response in 78 (31, 8%) patients and significant response in 122 (49, 8%) patients.

Keywords: Hemangioma; Congenital and infantile; Malformations; Laser; Surgery; Photodynamic therapy; 5-ALA

Introduction

Vascular anomalies are congenital anomalies of vascular development and cause various degrees of soft tissue abnormalities. These anomalies tend to occur most commonly in the head and neck and affect approximately 1 in 22 children [1,2]. The most recent classification of vascular anomalies ISSVA includes two main categories: vascular tumours (hemangiomas) and vascular malformations. Vascular tumours include 'infantile' and 'congenital' type haemangiomas; the former being the most common vascular tumour as well as vascular anomaly. Other types include pyogenic granuloma, tufted angiomas and haemangioendotheliomas, angiosarcomas [3-5].

Haemangiomas are more common in females and 80% occur in the head and neck [3,6]. Haemangiomas usually present isolated, multifocal or segmental result from endothelial cell hyperplasia. Infantile haemangiomas develop shortly after birth and follow the expected course of proliferation and prolonged involution. They are one of the most vascular tumour. The 'rarer' congenital haemangioma do not follow the same growth pattern but it does present at birth as the result of endothelial cell hyperplasia; and may rapidly involute or never involute. The causes of the aberrant and focal proliferation of endothelial cells in these lesions remain unclear [1,7].

Venous malformations are usually slow-flow vascular malformations composed of ecstatic venous channels that continue to grow throughout the patient's life. They commonly occur in the head and neck area, with a predilection for the oral cavity, airway and muscle groups. These lesions have unpredicted growth behavior when it comes to how much growth will occur or where; and many lesions expand well beyond their initial clinical boundaries and actual invasion of surrounding tissue may be occurring. These lesions are frequently symptomatic, depending on the locations involved and are usually obvious at birth. They fill with dependency and are compressible with variable color depending on the depth of involvement. Symptoms can be related to clot formation either from trauma or venous stasis and patients usually present with pain and swelling [8,9].

The various therapeutic options are available for vascular anomalies as well as the recent advances in psychosocial aspects of care, interventional radiology, laser and pharmacological therapy [10,11].

Photodynamic therapy

Photodynamic therapy (PDT) is a developing technology, used in the treatment of advanced tumour. The main application for PDT is to target tumour of the head and neck, gastrointestinal tract, pulmonary malignancies and skin pathologies. One advantageous feature of photodynamic therapy is that it does not cause damage to nerves (cold photochemical reaction); this has led to its use in the treatment of benign neoplasms [12,13].

The effects of PDT are a result of the interaction between a photosensitizer, oxygen and light. PDT may be provided under local, regional or general anesthesia and it may be delivered by surface illumination or interstitial application, via inserted optical fibers. The photosensitizer, administered whether locally or systemically, is selectively taken up and retained by tissues with a high vascular flow rate. Activation by light of a specific wavelength results in the production of oxygen free radicals or singlet oxygen which leads to apoptosis and/or direct cell death, as well as vascular shut down and subsequent inflammatory/immunological response [4,14]. Traditionally, light is delivered to the target tissue by surface illumination, whereby an optic probe is held over the target tissue (distance 5 cm). It can penetrate up to a depth of 1 cm, when used with 5-ALA due to its wavelength and

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Figure 1: Capillary malformation upper eyebrow, lips subjected to PDT. Clinical evaluation reported 'good response' to the therapy. Radiological response was 'significant'.



Figure 2: Venous malformation lower eyelid subjected to PDT. Clinical evaluation was 'good response'.

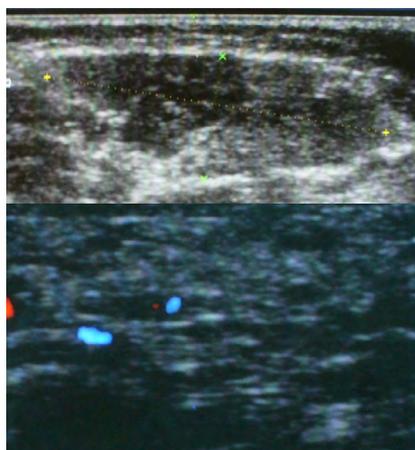


Figure 3: Radiological evaluation reported 'good response' to the therapy.

preoperative imaging, including computer tomography (CT), magnetic resonance imaging (MRI) and Ultrasound images has been shown to improve the accuracy of the technique. In this study we present the outcome following the management of vascular anomalies using photodynamic therapy. Patients' reports on quality of life with clinical and radiological evaluation were the main parameters used to assess the outcome (Figure 3).

Material and Methods

In this clinical study, 245 patients (54 males and 191 females) were referred to the general and maxilla-facial surgery departments, Tashkent medical academy, Uzbekistan (between 2009 and 2012) for treatment of a range of vascular anomalies. The mean age was $1,2 \pm 0,4$ years (Min 0.1, Max 34) with 89, 8% of the cohort being Central Asian, 7,7% Europeans, 2,4% different. The most common primary sites were the mid face, lower face, upper face, oral cavity and neck. Vascular anomalies included vascular tumour (infantile haemangiomas in 74 patients and congenital haemangiomas in 6 patients) and vascular malformations (venous malformation in 46 patients, lymphatic malformation in 57 patients and AV malformation in 62 patients) (Table 1).

Disease staging was carried out and showed that 210/245 patients were staged as having regional (extended) anomalies rather than local (localised) lesions. The anomaly volume was assessed using preoperative imaging (MRI, US). Seventy eight patients refused further conventional therapy (i.e. surgery) and elected to receive PDT, while 80 patients were not offered further conventional treatment and elected to receive PDT; the other 6 patients chose to undergo photodynamic therapy as the first intervention for their anomaly.

The patients' symptom-related disease included pain, bleeding, swelling, infection, disfigurement and breathing problems. One hundred eight patients were observed with chronic/recurrent pain which was associated with local pressure of the anomaly on nearby nerves. Forty six patients were observed bleeding which was mostly associated with trauma to their haemangiomas and AV malformations. Swelling problems were reported in 199 patients, while disfigurement was reported in 205 patients. Recurrent infection was identified in 63 patients, mostly in patients with lymphatic malformations. Breathing difficulties was associated with pathological growth in the nasal region in 5 patients. Since there is no validated assessment of quality of life tool for patients undergoing photodynamic therapy, our patients were asked only to report the nature of the complaint and not the severity (Table 2). No quality of life (QoL) questionnaires were applied in this study but merely patient's reports.

All patients were discussed at a multidisciplinary meeting involving surgeons, radiation and medical oncologists, interventional clinical radiologists and allied healthcare professionals. It was agreed to offer photodynamic therapy under general anesthesia, using 5-ALA as the photosensitising agent (200 mg/kg intravenous for malformation, 500 mg as 20% ointment was administered on skin surface, 3% solution inject into vascular anomaly for 6 hours (Min. 6, Max. 24) prior to treatment). Treatment was carried out at a fluence of 10–20 J/cm² and a standardised fluence rate of 100 mW/cm² [14]. This would allow the agent to accumulate in the pathological area which would increase effectiveness. Patients were usually kept in a side room (with a dim light) to avoid systemic photosensitisation. Intraoperatively, an ultrasound probe was used to examine the centre and periphery of the anomaly when assessing volume, depth, invasion of large vessels, hollow organs and/or hard tissue. This was followed by insertion of 18Gauge 70 mm

not properties of the photosensitiser. Interstitial PDT followed by the insertion of thin optical fibers into the needles, allows light maximal tissue illumination [15]. The application of iPDT in combination with

	No. (%)
Gender	
Male	54 (22)
Female	191 (78)
Age (years)	
Mean	1,2
Minimum–maximum	0,1-34
St. deviation	0,4
Race	
Central asian	220 (89,8)
European	19(7,7)
Different	6 (2,4)
Primary site	
Oral cavity	25 (10,2)
Upper face	37 (15,1)
Middle face	62 (25,3)
Lower face	46 (18,8)
Neck	38 (15,5)
Thorax, abdomen	13 (5,3)
Upper extremity	18 (7,3)
Lower extremity	6 (2,4)
Vascular anomalies	
Vascular tumours	
Infantile haemangioma	74 (30,2)
Congenital haemangioma	6 (2,4)
Vascular malformations	
Venous malformation	46 (18,8)
Lymphatic malformation	57 (23,3)
A–V malformation	62 (25,3)
Staging	
Local (localised)	35 (14,3)
Regional (extended)	210 (85,7)
Presentation	
Disfigurement	205 (83,7)
Swelling	199 (81,2)
Pain	108 (44,1)
Infection	63 (25,7)
Breathing Problems	5 (2,0)
Bleeding	46 (18,8)
Previous management	
Surgery	78 (31,8)
Embolisation	8 (3,3)
Sclerotherapy	46 (18,8)
Alcohol therapy	28 (11,4)
CO2 laser	68 (27,7)
Adjuvant chemoradiotherapy	11 (4,5)
None	6 (2,4)
Further conventional treatment rejected	165 (67,3)
Further treatment not offered	80 (32,7)
Round(s) of PDT	
1 round	39 (15,9)
2 rounds	13 (5,3)
3 rounds	159 (64,9)
4 rounds	11(4,5)
5 rounds	23 (9,4)
Follow up (months)	
Mean	21
Minimum–maximum	5–45
St. deviation	4,3

Table 1: Demographics of the 245 Patients with Vascular Anomalies.

long spinal needles under US-guidance into the target tissue. Great care was taken to ensure that the needles are inserted parallel to each other with 7-9 mm distance in between. If the treatment was close to a major blood vessel, a safety distance of 1 cm between the needle and the vessel was implemented.

An Iso-illumination treatment plan was carefully implemented and supervised by a senior physicist to ensure adequate light delivery to all suspect areas. A 635 nm diode laser was used for illumination. Diffuser fibres were used with/out bare polished tip fibres, with a core diameter of 400 µm, to deliver light. Light was then delivered from the fibres to the target tissue at 20 J per site. Tissues outside the target area were shielded completely to avoid photo activation by scattered or reflected light.

Pulse oximeters were repositioned at least every 30 minutes to avoid the risk of local skin burns and nail bed damage. All precautions were taken to avoid direct illumination of the patient with surgical lamps in theatres. Unplanned or emergency surgical interventions within 30 days from the photosensitiser administration were undertaken only if absolutely necessary and the potential benefits outweigh the risk to the patient. Precautions were applied to avoid exposure of skin and eyes to direct sunlight or bright indoor light during the first 15 days after injection. Patients were re-introduced to normal light gradually. No drug interactions have been observed.

The patients were discharged from hospital care at a mean of 5 days (Min 3, max 9) postoperatively. Patients were followed-up and asked to report on the outcome of their therapy if there is any improvement, no change or worsening of symptoms. Clinical assessment outcome was performed by a team of surgeons/physicians trained in photodynamic therapy at approximately 6 weeks postoperatively. The clinical assessment criterion was based on reduction of lesion size and improvement of the initial clinical symptoms. MRI imaging and US was performed 5–6 weeks postoperatively. Our radiological assessment parameters included: no response-progressive disease (increase in pathology size), no response-stable disease (no change in pathology size), minimal response (reduced size by <25%), moderate response (reduced size by <50%) and significant response (reduced size by 50-75%). Identification of peri-lesional inflammation, assessing response to PDT was also reported. The time between the rounds was 3-6 months, with treatment indicated when the patient becomes symptomatic. The mean follow-up for those patients was 21 months (Min 5, Max 45).

Statistical Analysis

This was performed using the SPSS 17 (statistical package for social scientists) by an independent statistician. The patients' data were entered onto proformas which were validated and checked by interval sampling. The fields included a range of clinical, operative and radiological parameters related to the outcome following photodynamic therapy. The results were cross tabulated and the Chi-squared statistic was used to test for differences in the incidence of outcome. Fisher's exact test was used for the analysis of contingency tables and therefore to measure the P-value.

Results

Eighty five out of one hundred eight patients who presented long-term or recurrent pain reported significant improvement of their symptoms ($P<0.001$); while the rest of the group reported no change. Also 43/46 patients with bleeding problems reported improvement ($P<0.001$), and no patient was reported with worsening bleeding

	No. (%)
a	
No response-stable (no change in pathology size), no response-progressing (increase in pathology size), minimal response (reduced size by <25%), moderate response (reduced size by <50%) and significant response (reduced size by 50–75%).	
Patient's report	
Pain problems	108
Improved ($P<0.001$)	85 (78,7)
No change	23 (21,2)
Worse	0 (0,0)
Bleeding problems	
Improved ($P<0.001$)	43 (93,5)
No change	3 (6,5)
Worse	0 (0,0)
Swelling problems	
Improved ($P<0.001$)	189 (95,0)
No change	10 (5,0)
Worse	0 (0,0)
Infection problems	
Improved ($P<0.001$)	61 (96,8)
No change	2 (3,2)
Worse	0 (0,0)
Disfigurement	
Improved ($P<0.001$)	176 (85,9)
No change	29 (14,1)
Worse	0 (0,0)
Breathing problems	
Improved ($P<0.001$)	3 (60,0)
No change	2 (40,0)
Worse	0 (0,0)
Clinical assessment	
No response	5 (2,0)
Minimal response	22 (9,0)
Moderate response	70 (28,6)
Good response	148 (60,4)
Radiologic assesment	
No response-stable	23 (9,4)
No response-progressing	5 (2,0)
Minimal response	37 (15,1)
Moderate response	78 (31,8)
Significant response	122 (49,8)
Complications	
Pain	12 (4,9)
Bleeding	5 (2,0)
Swelling	40 (16,3)
Infection	2 (0,8)
Skin burn	6 (2,4)
Skin ulceration	0 (0,0)
Sensory nerve injury	0 (0,0)
Motor nerve injury	0 (0,0)
Hypopigmentation	0(0)
Hyperpigmentation	6(2,4)

Table 2: Patients Responses pre and Post-PDT, Clinical and Radiological Assessments and Demographics.

episodes. Swelling improvement was observed in 189/199 patients and 176/205 patients reported improvement of their disfigurement; improvement in both parameters was significant ($P<0.001$). Infection rate was reduced in 61/63 patients who presented hemangioma and malformations ($P<0.001$). Breathing improvement was evident in 3/5 patients ($P<0.001$) (Table 2).

Clinical assessment showed that 148/245 patients had 'good response' to the treatment and 70/245 had 'moderate response'. Radiological assessment, comparing imaging 6-week post-PDT to the baseline, showed stable pathology with no change in size in 23/245 patients, minimal response (<25% reduction) in 37/245 patients, moderate response (<50% reduction) in 78/245 patients and significant response (50-75% reduction) in 122 patients. Five patients during the treatment showed no response with pathology progression (lymphangioma of the mid face) (Table 2, Figures 1 and 2).

Pain was reported by 12 patients and was mild-moderate. Bleeding was observed by 5 patients and no motor and sensory nerve injury was reported. Two patients reported postoperative infection and were treated with antimicrobials. No patient had skin ulceration/necrosis, skin burn was reported by 6 patients. Burn skin patients in sequence were observed hyper pigmentation (Table 2).

Discussion

Hemangioma prognosis established that haemangiomas resolve in 50% children by 7 of age. This case leads physicians to manage these patients in the conservative approach, but recent studies have showed that patients may present disease specific complication. This condition requires intervention and complete resolution in quite difficult to achieve. Problematic haemangiomas can cause severe functional issues including ulceration, disfigurement and affect breathing, swallowing and speech. Common locations for these problematic haemangiomas include face, ear, orbit, lower lip and airway [16].

Conventional management can include systemic or intra-lesional corticosteroids, beta blockers, chemotherapeutic agents, surgery, laser or a combination of these therapies. Where lesions are large, surgery can have marked adverse effect on form and function and due to difficulty in delineating, these lesions recurrences can be high. The side effects of chemotherapy are well known and radiotherapy carries the risk of inducing new tumour. Propranolol, a known non-selective beta-blocker, has been reported to induce regression in haemangiomas in newborns [17,18]. Sclerotherapy is the most common intervention in many centers around the world. Laser therapies have been reported as the most useful in the management of airway malformations and vesicular eruptions on mucosal surfaces. However, when it comes to complex lesions, surgery is always considered as the first option [19]. Resection of all diseased tissue is advocated as failure results in regrowth. Several studies have reported the use embolisation with varying substances (i.e. glue, coils and alcohol) in the management of AV malformations. This is mainly used in small and focal AV-malformations, but can be used in very large life-threatening AV- malformations 1, followed by microvascular free flaps to reconstruct the defect [4].

Photodynamic Therapy (PDT)

Since PDT is a non-heat generating process, there is no bystander tissue heating, and connective tissues, such as collagen and elastin, are largely unaffected. As a result, many tissues heal with little scarring in comparison to thermal treatment and hollow organs such as trachea, the gastrointestinal tract and major blood vessels that maintain their mechanical integrity [20]. The effectiveness of PDT depends on the dosimetric profile. Ideally one would quantify the distribution of the light fluence rate, the optical properties, the drug concentration and tissue oxygenation for PDT. The other advantage of PDT is that it can be repeated without cumulative toxicity. The success of PDT is dependent on upon the depth of necrosis being greater than the depth of the individual malformation. Thus, interstitial PDT represents is ideal,

in that it allows more effective treatment of the target tissue volume [17,20]. This clinical study highlights the advantage of ultrasound, in combination with PDT. It is relatively simple to perform, easily available and examinations are non-invasive. It is inexpensive, quick, and convenient and there are no known harmful effects, since it uses non-ionising radiation suited to the soft tissues and it does not cause any pain. Ultrasound can be used to guide the optical fibres to the appropriate disease volume, enabling more accurate evaluation of treatment doses [17,21].

The management of vascular anomalies continues to be extremely challenging. Although several modalities have been developed and the literature reports successful treatment in many, data from long term studies reports relapse in many and the need for re-treatment or another intervention. Photodynamic therapy is not superior to other modalities, but it is characterized by being one of the least invasive, being repeatable with no residual toxicity and with a minimal bystander effect on the overall tissue architect and integrity as well as nerves. The growing body of evidence regarding its efficacy, the increasing use of image guided PDT, and the innate minimally invasive characteristics of PDT suggest that it should become an important addition to the various techniques used in the management of vascular anomalies.

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