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Assessment of Treatment of Actinic Keratosis Using Photodynamic Therapy

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Abstract:
Background:Actinic Keratosis (AK) lesions are cutaneous neoplasms develop as a result of chronic UV exposure.Photodynamic therapy (PDT) is used in conjunction with molecular oxygen to elicit cell death (phototoxicity).
Aim of work: Investigation of complete responses ratesafter daylight photodynamic therapy using methylene blue versus cryotherapy in the treatment of AKs.
Patients and Methods:We conducted out an experimental study at Dermatology, Venereology and Andrology Department, Zagazig University Hospitals on 30 AK patients suitable for daylight photodynamic therapy with methylene blue (DL-MB/PDT) (liposomal-loaded methylene blue gel 10%) in 15 patients (group I) and cryotherapy in the other 15 patients (group II).
Results: there was no statistical significant difference between groups I and II in response to treatment.Group I showed 86.7% partial response and 13.3% complete response and group II showed partial response 80% and complete response 20%. Absence of response to daylight-MB/PDT was not observed. In our study, there was no statistically significant relation between response and demographic, history and clinical data in group I and group II.
Conclusion: In conclusion, MB/PDT is a useful and safe therapeutic method for treating AKs, which had advantages over cryotherapy. We believe that MB is an excellent alternative as the advantages of MB include its high safety profile, low cost as it is routinely available in hospital pharmacies.
Key words: Actinic Keratosis, daylight photodynamic therapy with methylene blue (DL-MB/PDT).

Introduction

Skin changes in response to the sun have dramatically increased in the last 50 years because of aging of the population and the expanded time people spend outdoors, which increases their exposure to ultraviolet (UV) radiation from the sun. Skin cancer accounts for nearly half of all cancers in the United States. More than 2 million cases of non-Melanoma Skin Cancer (NMSC) are reported in this country each year **(1)**.

Actinic Keratosis (AK) lesions are cutaneous neoplasms composed of proliferative, transformed keratinocytes that develop as a result of chronic UV exposure. AK lesions represent the earliest manifestation of NMSC, as they have not acquired the full complement of chromosomal aberrations and invasive growth characteristics that are associated with invasive Squamous Cell Carcinoma (SCC) **(1)**.

Photodynamic therapy (PDT), sometimes-called photochemotherapy, is a form of phototherapy involving light and a photosensitizing chemical substance, used in conjunction with molecular oxygen to elicit cell death (phototoxicity). PDT has proven ability to kill microbial cells, including bacteria, fungi and viruses **(2).**

Methylene blue (MB), also known as methylthioninium chloride, is a hydrophilic phenothiazine derivative. It is a photosensitizer with light absorption at 660 nm. Moreover, MB is an inexpensive photosensitizer. MB is used for antimicrobial photodynamic therapy (APDT) and is used as a potent PDT drug for local treatment of periodontal diseases, because of its efficiency against a broad spectrum of microbes including bacteria, fungi, and viruses. The efficiency of MB-APDT has also been demonstrated on an antibiotic resistant polymicrobial biofilms of Pseudomonas aeruginosa and Methicillin-resistant Staphylococcus aureus (MRSA) in a maxillary sinus model. The photosensitizer used consisted of MB suspended in double distilled water at a concentration of 10 mg/mL. As light source a diode laser operating at 655 nm was used. **(3)**.

DL-PDT may be used for treatment of Grade I&II, thin nonhyperkeratotic AK lesions on the face and scalp as well as for patients with large areas of actinic damage. DL-PDT is not recommended for Grade III (hyperkeratotic lesions), although pretreatment with curettage or other modalities such as keratolytics (e.g., urea, lactic acid, or salicylic acid creams) to reduce hyperkeratosis may be considered **(1)**.

We aimed at this work to investigate complete responses rates after daylight photodynamic therapy using methylene blue versus cryotherapy in the treatment of AKs.

Patients and Methods

This experimental study was conducted out at Dermatology, Venereology and Andrology Department, Zagazig University Hospitals on 30 patients. The period of this study was from May 2019 to May 2020. The 30 patients were of both sexes and were divided into 2 groups. Group I consisted of 15 patients treated with daylight photodynamic with methylene blue (DL-MB/PDT) (liposomal –loaded methylene blue gel 10%) and group II consisted of 15 patients treated with cryotherapy. This study had the approval of the institutional review board (IRB) at Zagazig university.

Inclusion criteria:

Patients had at least multiple actinic keratosis lesions on the face or scalp, and no treatment within the last 4 weeks. The diagnosis was based on clinical assessment and dermoscopy. Dermoscopic finding which can be found in actinic keratosis; redpseudonetwork, scales, targetoid like appearance and rosette sign.

Exclusion criteria:

Patients receiving regular ultraviolet therapy, Patients with pigmented lesions in the target area or porphyria, Photodermatosis or patients with photosensitive diseases such as photosensetive dermatoses, solar dermatitis, sunburn, solar urticaria and chronic actinic dermatitis), Other patients with polymorphus light eruption have been excluded from the study.

Methods:

An informed consent was obtained from each patient after informing him or her about the technical and scientific basis of the research project, the steps of the procedure and the expected effects or possible complications.

All the patients of the two groups were subjected to the following:

1- History taking. A purposely-designed sheet was performed for all patients in this study, including:

- Personal history including (name, age, sex, residence, educational level, marital status and special habit of medical importance).
- Present history.
- Drug history of phototoxic drugs and arsenic therapy.
- Past history of systemic diseases.

2- General clinical examination to rule out any systemic disease.

3- Complete dermatological examination to assess grade of actinic keratosis clinically and for presence of any other skin problems.

Dermoscopic examination before treatment and at the end of the study

Treatment procedure:

Before treatment for both groups loose crusts and debris were removed from the lesion using a small curette and the surface was gently scrapped.As actinic keratosis has three grades: grade I, easily visible and slightly palpable , grade II, easily visible and palpable and grade III, frankly visible and hyperkeratotic. Up to 10 lesions were treated at single treatment session

Group I (DL_MB/PDT):

Topical MB gel 10% was applied in a layer approximately 0.5-1 mm thick over the lesion area (avoiding intervening normal skin) without occlusion and left for 15 minutes. Patients were instructed to stay outdoors exposing their lesions and the adjacent area to daylight continuously for 1 hours from 11 am to 2 am in the garden of the hospital. At the end of daylight exposure, patients wiped off any residual gel with alcohol-soaked towel. A single treatment session was done.

The characteristic color of MB is caused by the strong absorption band in the 550-700 nm region with strong visible light absorption is at 609 and 688 nm. Peak absorption is at 688 nm, hence daylight MB activation is mainly by orange-red (590–750 nm) light

Group II (cryotherapy):

We used the liquid nitrogen as cryogen. We used the spray technique as the nozzle tip of the spray gun is held about 1 to1.5 cm from the lesion. We used the liquid nitrogen on the lesion until an ice ball is formed and white rim bout 1-2 mm outside the marked outline of the lesion is formed.Afterfreezing,tissue is permitted to thaw spontaneously.This freeze-thaw cycle(actual freezing of a lesion plus thawing of it) and we made another cycle after few seconds

Clinical assessment:

For both groups safety and clinical assessments were performed by two separate observers at baseline, immediately at 24 hours, at 72 hours, in weeks 1, 4, 8 and 12 after treatment.Photographs for patients taken before start of treatment and at the end of follow up. Dermoscopic examination was documented by photograph before treatment and at the end of follow up. Clinical response was defined as the percentage reduction of pretreatment lesion area and rated as follows:

- Complete response (CR): Completely cleared with no evidence of adherent scale on the surface of the treated skin when visualized,no erythema and skin return to normal in each lesion site.
- Partial response (PR): ≥ 50% reduction in size of lesion,slight adherent scale,slight erythema and slight wheal in each lesion.
- No response (NR): < 50% reduction in size of lesion,no more change in erythema, scale and wheal (Edward W et al.,2001).
- Dermoscopic response depended on when there were no features of red pseudo-network, scales, targetoid-like appearance and rosette sign.

Immediately after treatment for both groups, and at each subsequent visit, treatment sites were evaluated for:

- Objective changes in erythema, edema, wheal, vesiculation, ulceration, hemorrhage, and necrosis on a graded scale (0: none; 1: minimal; 2: moderate; 3: severe).
- Subjective assessment of patient discomfort from pain, burning, stinging and itching was graded (0; none / 1; minimal / 2; moderate / 3; severe).

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 25.0. Qualitative data were represented as frequencies and relative percentages.

Chi square test was used to calculate difference between qualitative variables.

Results

There were no statistically significant differences between the studied groups in age or sex distribution**(Figure 1).**

There was no statistically significant difference between groups I and II in disease duration, site or grade**(Figure 2).**

There was no statistically significant difference between groups I and II in response to treatment, and the two groups showed great response **(Figure 3).**

There was no statistically significant relation between response and demographic, history and clinical data in group I **(Table 1).**

There was no statistically significant relation between response and demographic, history and clinical data in group II**(Table 2).**

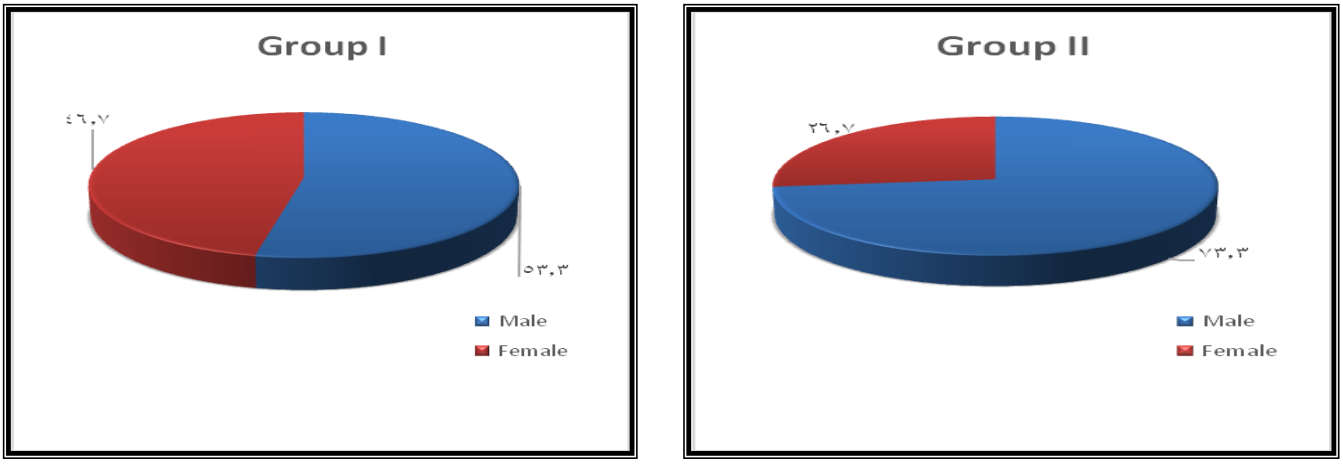

Figure (1): Sex distribution among the studied groups.

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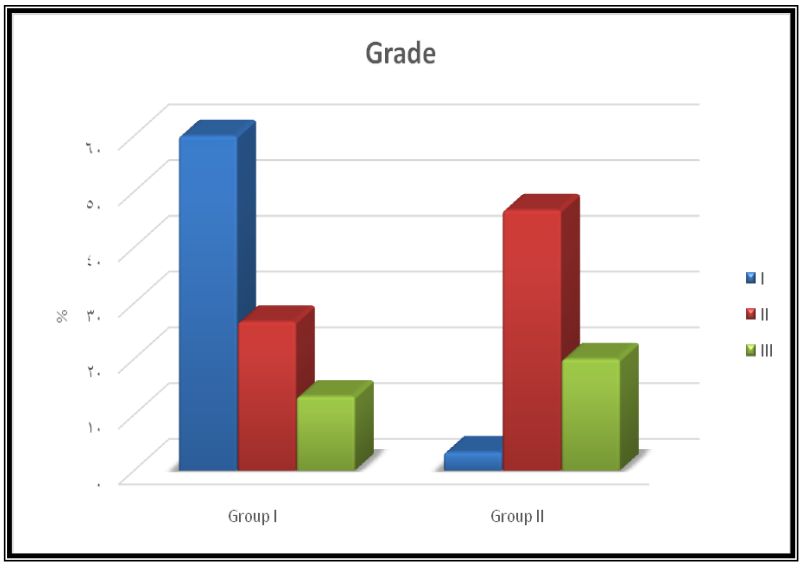

Figure (2): Grade of disease among the studied groups.

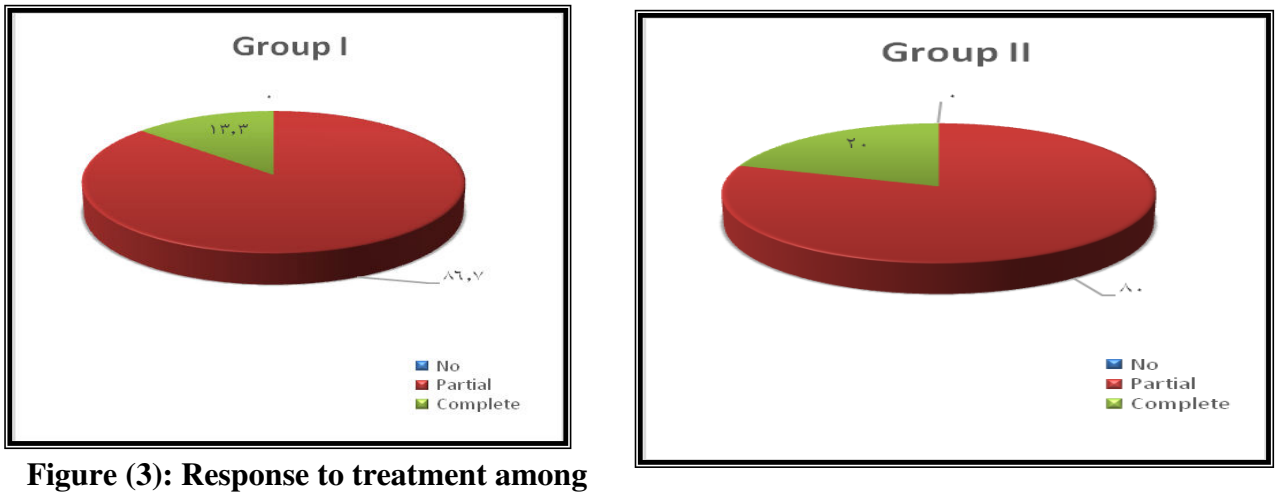

Figure (3): Response to treatment among the studied groups.

Table 1: Relation between response and demographic, history and clinical data in group I

Variable		Partial (*n*=13)		Complete (*n*=2)		t	P
Age: (years)	Mean ± SD Range	61.62 ± 2.10 60 - 65		63.5 ± 2.12 62 - 65		1.18	0.26 NS
Duration (years)	Mean ± SD Range	3.15 ± 1.34 2 - 5		2.5 ± 0.71 2 - 3		1.32	0.41 NS
Variable		No	%	No	%	χ^2	P
Sex:	Female Male	6 7	46.2 53.8	1 1	50 50	0.01	0.92 NS
Systemic disease:	No HPT DM	7 3 3	53.8 23.1 23.1	1 0 1	50 0 50	0.94	0.63 NS
Site:	Face Scalp	12 1	92.3 7.7	2 0	100 0	0.17	0.69 NS
Grade:	I	7	53.8	2	100		

	II	4	30.8	0	0	1.54	0.46
	III	2	15.4	0	0		NS

Table 2: Relation between response and demographic, history and clinical data in group II.

Variable		Partial (*n*=12)		Complete (*n*=3)		t	P
Age: (years)	Mean ± SD	62 ± 2.21		61.67 ± 2.89		0.22	0.83
	Range	60 - 65		60 - 65			NS
Duration (years)	Mean ± SD	2.75 ± 0.45		2.67 ± 0.58		0.27	0.79
	Range	2 - 3		2 - 3			NS
Variable		No	%	No	%	χ^2	P
Sex:	Female	3	25	1	33.3	0.09	0.77
	Male	9	75	2	66.7		NS
Systemic disease:	No	6	50	1	33.3		
	HPT	3	25	1	33.3	0.27	0.88
	DM	3	25	1	33.3		NS
Site:	Face	7	58.3	3	100		
	Scalp	3	25	0	0	1.88	0.39
	Ear	2	16.7	0	0		NS
Grade:	I	4	33.3	1	33.3		
	II	6	50	1	33.3	0.48	0.79
	III	2	16.7	1	33.3		NS
Side effect:	No	9	75	2	66.7	0.09	0.77
	Hypopigmentation	3	25	1	33.3		NS

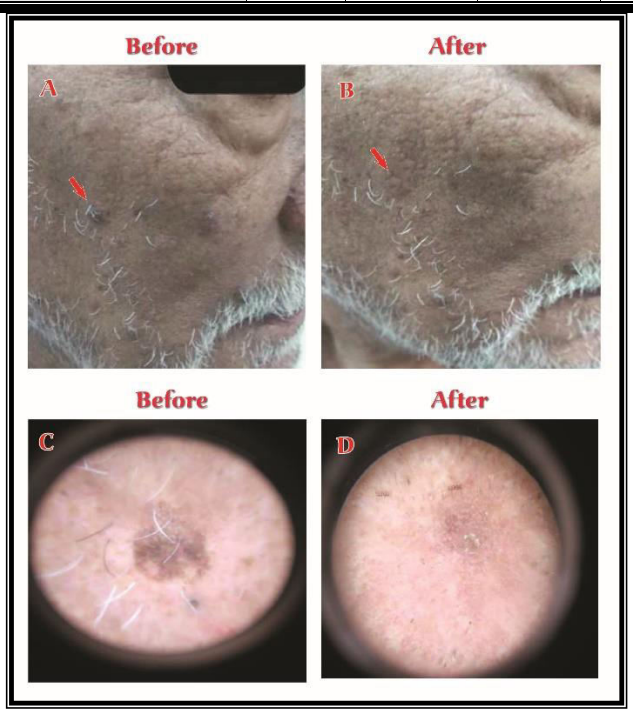

Figure (4): Male patient of 64 years old with an actinic keratosis on face showed partial response after a single session of daylight photodynamic with methylene blue.

- **(C)** Showing dermoscopic picture, targetoid appearance and rosette sign.
- **(D)** Showing dermoscopic picture, partial disappearence of targetoid appearance and rosette sign

Discussion

AKs are a global problem, causing huge economic losses on account of their high prevalence. It has been reported that the prevalence is around 50% in Australia and 11–34% in the Northern Hemisphere. Several topical treatment options for AKs are available, including topical chemotherapy, curettage, photodynamic therapy (PDT), and cryotherapy **(4)**.

Conventional PDT (CPDT) is one of the most popular PDT therapies and is characterized by the topical application of methyl aminolevulinate cream. CPDT is suitable for treating thin, nonhyperkeratotic AKs with large skin areas on the face or scalp, which yields a high response rate and satisfactory cosmetic outcome compared with other conventional treatment options **(5)**.

The present work performed on 30 patients treated with single session. We divided them into two groups, the first group consisted of 15 patients treated with daylight photodynamic with methylene blue, and the second group consisted of 15 patients treated with cryotherapy. The study aimed to compare between the efficacy of daylight-photodynamic with methylene blue and cryotherapy in treatment of actinic keratosis.

The present work showed that there was no statistically significant difference between groups I and II in response to treatment. All the cases showed different grades of response. There were 13 cases in group I showing partial response (86.7%) compared to 12 cases in the second group who showing partial response (80%). There were 2 cases in group I showing complete response (13.3%) compared to 3 cases in group II (20%). Our study achieved a higher partial respone for grade I (53.8%) and a lower partial response for grade IIAKs (30.8%) due to thinner skin in grade I than grade II.

It is noteworthy to menthion that**Sotiriou et al. (6)** used methyl-aminolevulinic as photosensetizer in a single treatment seesion for actinic keratosis. After following up of three months could reach a 83.8% partial response in grade I actinic keratosis and 70% partial response in grade II. This could be attributed to large number of patients they used (46 patients) and they used the lux apparatus to measure the suitable wavelength of daylight to allow high penetration of the photosensetizer. Another explanation could be due to the usage of methyl-aminolevulinicas aphotosensetizer.

Conclusion

In conclusion, DL-MB/PDT is a useful and safe therapeutic method for treating AKs, which had advantages over cryotherapy. We believe that MB is an excellent alternative as the advantages of MB include its high safety profile, low cost as it is routinely available in hospital pharmacies

Therefore, our results demonstrated that DL-MB/PDT has great potential to become a novel treatment option for AKs, especially in patients who cannot tolerate intense pain, helping in guiding physicians to optimize treatment strategies

Conflict of interest: The authors declare no conflict of interest.

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