Artigo de Revisão

PUVA Oral Versus Banho PUVA na Psoríase em Placas: Um Estudo Comparativo de Eficácia

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RESUMO – **Introdução**: A fototerapia é uma terapêutica bem consolidada no tratamento da psoríase, com uma relação risco-benefício bastante favorável. A fotoquimioterapia envolve a administração de psoraleno *per os* (PUVA oral) ou tópico (banho PUVA), antes da irradiação por UVA. A administração oral de psoraleno pode causar efeitos adversos, enquanto o banho PUVA tem a vantagem de diminuir a toxicidade sistémica e os efeitos adversos do psoraleno. O nosso estudo teve como principal objectivo comparar a eficácia entre as duas modalidades de PUVA. **Material e Métodos**: Estudo retrospetivo, aplicado aos doentes com psoríase em placas tratados com PUVA no nosso serviço de Dermatologia, entre janeiro 2001 e dezembro 2016. **Resultados**: Foram realizados 81 ciclos de tratamentos com PUVA oral e 38 com banho PUVA, correspondendo a 68 e 26 doentes, respetivamente. A idade média foi de 50,6 anos. No primeiro grupo, o PASI 75 foi atingido em 68 casos (89,5%), e no grupo de banho PUVA em 26 (74,3%), com $p = 0,05$. A dose média para atingir o PASI 75 no grupo PUVA oral foi de 113,1 J/cm^2 e no grupo banho PUVA de 69,8 J/cm^2. No grupo PUVA oral, o número médio de sessões realizadas para atingir PASI 75 foi de 23,31, e no grupo banho PUVA 17,58. **Conclusão**: Embora exija equipamento especializado e mais tempo de execução, o banho PUVA pode ser considerado ainda um dos tratamentos mais eficazes na psoríase, sobretudo num grupo particular de doentes não candidatos a terapêuticas sistémicas.
PALAVRAS-CHAVE – Administração Oral; Administração Tópica; Banhos; Psoríase/tratamento; Terapia PUVA.

Oral PUVA Versus Bath PUVA in Chronic Plaque Psoriasis: A Comparative Study of Efficacy

ABSTRACT – ***Introduction:*** *Phototherapy has long been recognized as beneficial for psoriasis treatment, with a favorable risk-benefit relation. Photochemotherapy comprises the use of psoralen, either orally (oral PUVA) or topically (bath PUVA), prior to UVA irradiation. Oral administration of psoralen may lead to short or long-term side effects. Bath PUVA is particularly useful to minimize systemic toxicity and psoralen side effects. The aim of this study was to compare the effectiveness of these two PUVA modalities.* ***Material and Methods:*** *A retrospective review of patients with chronic plaque psoriasis treated with PUVA therapy (oral and bath) in our dermatology department, between January 2001 and December 2016.* ***Results:*** *We performed 81 treatments with oral PUVA and 38 treatments with bath PUVA, in 68 and 26 patients, respectively. The mean age of the patients was 50,6 years. Oral PUVA group achieved PASI 75 in 68 cases (89.5%), and bath PUVA group in 26 (74.3%), with p-value=0 .05. The mean total dose needed to achieve PASI 75 in the oral PUVA group was 113.1 J/cm^2 and in the bath PUVA group was 69.8 J/cm^2. The mean number of sessions performed to achieve remission in the oral PUVA group was 23.31, and in the bath PUVA group was 17.58.* ***Conclusion:*** *Despite requiring specialized equipment and being more time consuming, bath PUVA represents one of the most effective therapies available for psoriasis and it should be considered as a treatment option for patients who are not candidates for systemic treatment.*
KEYWORDS – *Administration, Oral; Administration, Topical; Baths; PUVA Therapy/methods; Psoriasis/therapy.*

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Artigo de Revisão

INTRODUCTION

Phototherapy is a well-known treatment for several cutaneous inflammatory diseases. In psoriasis, phototherapy has a particularly favorable risk-benefit relation. However, the use of phototherapy/photochemotherapy in dermatologic departments has declined because of logistic issues and the development of new systemic drugs.

The mechanisms of the action of phototherapy in psoriasis include an effect on cell surface receptors with modification of the cytokine profile and secretion of mediators with anti-inflammatory and immunosuppressive properties, antiproliferative effects and induction of apoptosis in target and effector cells, such as epidermal and dermal T cells, keratinocytes and also to a lesser extent Langerhans cells.[1]

Photochemotherapy includes the administration of a psoralen, which is a photoactive furocoumarin that after UV irradiation binds both DNA chains, interfering with the process of cell division, thus enhancing the effect of phototherapy. Psoralen can be administered either orally (oral PUVA) or topically (bath PUVA), prior to irradiation in the UVA cabin. Oral administration of psoralen may lead to nausea or long-term side effects (cataracts, skin tumors, skin aging). Bath PUVA is particularly useful to minimize psoralen systemic toxicity and side effects.[2-5] The above-mentioned advantages of bath PUVA motivated us to study and compare this treatment modality with more widely used oral PUVA.

MATERIAL AND METHODS

We conducted a retrospective review of the patients with plaque psoriasis treated with PUVA therapy (oral and bath) in our dermatology department, between January 2001 and December 2016.

Treatment protocol: The oral PUVA group received 8-methoxypsoralen capsules (0.3-0.5 mg/kg) 2 hours prior to UVA irradiation. Patients treated with bath PUVA were immersed during 15 minutes in a 0.5 mg/L solution of 8-methoxypsoralen, followed by UVA irradiation within minutes. In both groups, the initial UVA dose was 0.5 J/cm^2 and the dose was increased by 0.5 J/cm^2 with each session. Both oral PUVA patients and bath PUVA patients were treated 3 times per week until complete clearing.

PASI score was used to assess disease severity and evaluate efficacy of therapy. Achievement of PASI 75 (75% reduction in the PASI score), considered a successful outcome. The 2 groups were compared concerning the number of UV sessions and UV dose needed to reach a PASI 75, as well as the length of duration of treatment response.

Statistical analysis was performed with SPSS Statistics (v. 23; IBM SPSS). The sample was characterized by descriptive and inferential statistical methods. Means were compared by the Student t-test when the conditions of normality and homogeneity of variances were fulfilled. For the analysis of 2 independent samples, without normal distribution, the Mann-Whitney U test was used to compare the medians. Nominal data were analyzed by Pearson's $\chi 2$ test and, in situations with low number of cells, Fisher's exact test was used. Statistical significance was considered when p-value was equal or below 0.05.

The local hospital ethics committee and the Portuguese National Data Protection authority approved the study.

RESULTS

We performed 81 treatments with oral PUVA and 38 treatments with bath PUVA, in 68 and 26 patients, respectively. The mean age of the patients was 50.6 years (SD = 12.84 years) (49.9 years in the oral PUVA group versus 52.0 years in the bath PUVA group).

The mean initial psoriasis area and severity index (PASI) was similar in both groups, 21.0 in oral PUVA group and 22.5 in bath PUVA group, expressing the moderate to high disease severity within the entire sample of treated patients.

Oral PUVA group achieved PASI 75 in 68 cases (89.5%), and bath PUVA group in 26 (74.3%), with a p-value = 0.05. The inferential statistical analysis showed that the effectiveness of PUVA is independent of the treatment modality.

The mean total dose needed to achieve PASI 75 was 113.1 J/cm^2 (median 97.5) in oral PUVA group and 69.8 J/cm^2 (median 46.2) in bath PUVA group, p = 0.001 (Fig. 1). The mean number of sessions performed to achieve remission was 23.31 (SD = 8.5) in the oral PUVA group, and 17.58 (SD = 10.0) in the bath PUVA group, p = 0.008. In bath PUVA group, PASI 75 was achieved with 1.5 to 9.94 less sessions (in average 5.7 sessions), comparing to oral PUVA group.

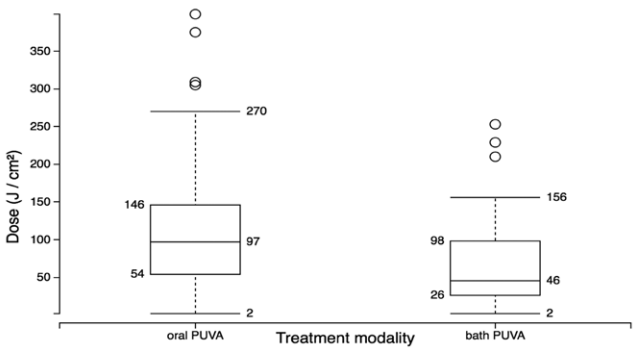

Figure 1 - Diagram of extremes and quartiles for the dose of UVA administered in oral PUVA group (n=81) and bath PUVA group (n=38).

The study evaluated also remission duration, i.e. interval between the complete or almost complete clearance and the reappearance of lesions. The study sample was divided into 4 groups according to remission interval: 1 to 3 months, 3.5 to 6 months, 6.5 to 12 months and remission for more than 12 months. Comparing the oral PUVA group with bath PUVA group, there was no difference in remission intervals in both groups (p = 0.766). The results are summarized in the Table 1.

Table 1 - Results of the study highlighting the differences between the two treatment groups.

	Total sample	Oral PUVA	Bath PUVA	*p*-value
Course of treatments	119	81	38	
Age	50.6 (±12.84)	49.9 (±14.3)	52.0 (±9.15)	0.356*
PASI	21.6 (9.5)	21.0 (10.0)	22.5 (8.8)	0.432*
UVA dose (J/cm²)	99.3 (7.1) Me=81	113.1 (8.9) Me=97.5	69.8 (10.4) Me=46.2	0.001*
No. of sessions per course	21.0 (9.6)	23.31	17.58	0.008**
Efficacy (PASI 75)	94 (84.7%)	68 (89.5%)	26 (74.3%)	0.050#
Remission duration 1 to 3 months 3.5 to 6 months 6.5 to 12 months > 12 months	 n=14 (17.1%) n=25 (30.5%) n=25 (30.5%) n=18 (22.0%)	 n=12 (20.0%) n=15 (25.0%) n=18 (30.0%) n=15 (25.0%)	 n=2 (9.1%) n=10 (45.5%) n=7 (31.8%) n=3 (13.6%)	0.766*

Fisher's exact test (1 sample); * Mann-Whitney U test (2 independent samples without normal distribution); ** T test for equal means, bilateral significance.

DISCUSSION

The present study confirmed the effectiveness of PUVA in the treatment of psoriasis.[6] Comparing the two treatment modalities, bath and oral PUVA, we found equal/similar efficacy. There are few studies comparing efficacy of the two PUVA treatment modalities in chronic plaque psoriasis. The only prospective randomized trial comparing the efficacy of oral and bath PUVA, conducted by Berneburg *et al* in 2013, concluded overall excellent effectiveness of PUVA with no difference in the two studied groups.[6] Other smaller, comparative studies showed similar effectiveness of bath and systemic PUVA, nonetheless, as in our work, the studies highlight that patients treated with bath PUVA required an inferior number of sessions and less total dose to clear the lesions.[7-11] Additionally, patients who fail to respond to oral PUVA may benefit from switching to bath PUVA.[10] However, in the studies no standard methodology has been used, namely in terms of psoralen concentration used for bath PUVA (0.4 mg/L, 1 mg/L, 3.7 mg/L to 4.6 mg/L). Psoralen concentration used in our study was 0.5 mg/L, which despite of being lower than in most studies still lead to significant effectiveness.

Attending to patients´ preferences, there might be slight tendency to bath PUVA when the patient is involved in the treatment modality decision. Alshiyab *et al* studied the treatment preferences in 99 patients treated with photochemotherapy. Of the whole group, 55% preferred bath PUVA, with a clearer preference among females (61%). Moreover, within the subgroup of patients that had previously received bath PUVA therapy, 75% preferred to be treated again with bath PUVA.[7,11]

Safety of bath PUVA was highlighted in several studies.[4-8] Skin cancer, the well-known long term side effects of oral PUVA, was investigated in an analysis of a Scandinavian population treated with bath PUVA. The authors did not find an increased risk of skin cancer with bath PUVA, therefore suggesting this an important advantage of bath PUVA over oral PUVA.[4,5] Topical administration of psoralen may still cause immediate or short-term side effects, similarly to oral PUVA, such as erythema, blistering and hyperpigmentation. In our revision, due to the design of the study, it was not possible to access the short- and long-term cutaneous side effects in the sample.

The list of advantages of bath PUVA continues. Patients with comorbidities such as hepatic dysfunction, ocular disease or concomitant medication interfering with oral psoralen, such as warfarin, may benefit particularly from topical psoralen use.[6-8,12] Furthermore, in patients with moderate to severe plaque psoriasis who present contraindication to biologic treatment, such as history of cancer or demyelinating disease, bath PUVA may represent a good therapeutic option.

Pointing out all the advantages of bath PUVA to oral PUVA, one must not forget the logistic issues of bath therapy. This treatment modality requires specific equipment, such as a proper room with bathtub and trained health care personnel. Also, bath PUVA is more time consuming in comparison to oral PUVA and may not be suitable for patients with decreased mobility.

CONCLUSION

Bath PUVA, as one of the most effective therapies available for psoriasis, is still commonly used in Scandinavian

Artigo de Revisão

countries for moderate to severe plaque psoriasis in order to reduce the systemic psoralen toxicity. In Portugal there are few hospital facilities equipped with bathtub for bath PUVA. To the best of our knowledge, our department of Dermatology is the only in Portugal who continues using bath PUVA for chronic plaque psoriasis, especially for patients with associated comorbidities. Even if we take into consideration the special equipment and more time consuming character of bath PUVA treatment, its benefits clearly outweigh these minor logistic issues. As a result, we strongly recommend bath PUVA treatment for patients with chronic plaque psoriasis who are not candidates for systemic treatment.

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