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Comparison of Hexaminolevulinate Based Flexible and Rigid Fluorescence Cystoscopy with Rigid White Light Cystoscopy in Bladder Cancer: Results of a Prospective Phase II Study

J. Alfred Witjes*, Paula M.J. Moonen, Antoine G. van der Heijden

Department of Urology, University Medical Centre, St Radboud, Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

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Abstract

Introduction and Objective: Several studies have shown that rigid fluorescence cystoscopy (RFC) with hexaminolevulinate (HAL) is superior to standard rigid white light (RWLC) cystoscopy in diagnosing bladder tumours, with a clinically relevant impact on the patient's management. These studies, however, have been done with rigid cystoscopes. We carried out a study to evaluate whether the technique of fluorescence cystoscopy with HAL was also feasible with a specially designed flexible fluorescence cystoscope (FFC).

Methods: 20 patients with known or suspected bladder cancer were included in a comparative within patient controlled Phase II study. All patients signed informed consent. All patients received 50 ml of HAL (Hexvix®) 8 mM 1 h prior to transurethral resection. Using a D-light-C® system (Storz, Germany), FFC and RFC were performed followed by RWLC. All lesions visible during these three cystoscopies were mapped, taped and resected.

Results: In these 20 patients (mean age 71 years (49–89), 3 females) mean HAL instillation time was 81 min. Overall 27 histologically confirmed lesions were found in 19 patients. Detection rates in these 19 patients were 14 with FFC, 17 with RFC and 15 with RWLC. Of the 27 lesions 19 were detected with FFC, 23 with RFC and 20 with RWLC. Overall fluorescence intensity using the flexible system was 76% (30–147%) as compared to RFC using a visual analogue score. No side effects were noted which were attributable to HAL.

Conclusion: The use of FFC is feasible and seems to be comparable to RWLC and slightly inferior to RFC. Larger studies should determine the role of flexible fluorescence cystoscopy.

Keywords: Bladder cancer; Diagnosis; Fluorescence cystoscopy; Flexible cystoscopy; HAL

1. Introduction

Bladder cancer is among the most frequent cancers in men. Superficial bladder cancer is characterized by a high recurrence rate after the initial treatment, transurethral resection with or without additional intravesical therapy. Follow up of these patients is typically done with periodic urinary cytology and cystoscopy. Although urinary markers have been studied for almost a decade now, they still lack sufficient sensitivity and specificity to apply them in clinical practice. Moreover, patients appear to have more faith in a cystoscopy than in a urinary marker analysis [1]. However, the sensitivity of cystoscopy for papillary tumours is disappointing, as was also concluded from a large EORTC meta-analysis published recently [2,3]. The tumours that have been missed during the resection will account for at least part of the frequent recurrences after initial treatment. An even bigger problem is the diagnosis of carcinoma in situ (CIS), per definition a flat urothelial lesion. Even the use of random biopsies does not result

* Corresponding author. Tel. +31 24 3616712; fax: +31 24 3541031.
E-mail address: f.witjes@uro.azn.nl (J.A. Witjes).

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in a clinically relevant improvement in the diagnosis of CIS [4,5].

To improve the sensitivity of cystoscopy, especially of CIS, fluorescence cystoscopy has been studied extensively the last years [6]. Currently, the intravesical administration of new generation photo sensitizers, such as hexaminolevulinate hydrochloride (HAL), has proven to be safe and significantly improves the detection rate of papillary tumours and CIS as compared to white light cystoscopy only [7], with a clinically relevant impact on the patient's management [8]. However, all studies evaluating the value of fluorescence cystoscopy have been done with rigid cystoscopy instruments, which are typically used in the management of recurrences, transurethral resections and biopsies. Since outpatient cystoscopic follow up nowadays is predominantly done with flexible cystoscopes, and outpatient detection of CIS is also an important issue, we carried out a study to evaluate whether the technique of fluorescence cystoscopy with HAL is also feasible with a specially designed blue light flexible cystoscope.

2. Material and methods

20 patients with known or suspected bladder cancer, based on outpatient cystoscopy findings or abnormal cytology, were included in a comparative within patient controlled phase II study between January and March 2004. All patients had given written informed consent. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki 1964, including the most recent amendment (Edinburgh, Scotland, 2000) and after written approval of the local medical ethical committee.

Methods have been described in detail before [7]. In short patients with gross hematuria, and those with intravesical therapy within 3 months prior to the study were excluded. All patients received 50 ml of HAL 8 mM 1 h prior to transurethral resection of the known tumour. After emptying of the bladder inspection and mapping of all lesions and suspicious areas was done by two investigators with extensive experience with this method based on previous studies (JAW, AGvdH) [7,8]. This was first done with a flexible D-light cystoscopy system flexible fluorescence cystoscopy = FFC), secondly with a rigid D-light cystoscopy system (rigid fluorescence cystoscopy = RFC) and finally with normal white light cystoscopy (rigid white light cystoscopy = RWLC), which was also used for resection and biopsies of suspicious areas. All three procedures were carried out in every patient. All equipment used was from Karl Storz (Tuttlingen, Germany). The properties of the blue light flexible scopes are similar to the white light flexible scopes of Karl Storz, namely 15.5 Fr outer diameter, 7 Fr instrument channel, a working length of 35 cm, and deflection of +210 to −120 degrees. The whole procedure was documented in the CRF and with video. Tissue was examined and staged/graded by the local pathologist.

Adverse events (AEs) were recorded until hospital discharge, or followed until resolved.

3. Results

20 patients were included in this study, of which 3 were female. The mean age was 71 years (49–89). 10 patients had primary lesions, 7 single lesions. 7 patients had prior intravesical chemotherapy or BCG for superficial papillary tumours. 5 patients had negative cytology (all TaG2). Mean HAL instillation time was 81 min.

Of these 20 patients with suspected bladder cancer during outpatient cystoscopy, bladder cancer was histologically proven in 19. In these 19 patients 27 lesions were found. Six patients had a solitary pTaG2, two had 2 pTaG2 tumours, four patients had a pTaG3, pT1G3 with CIS, pT2G3 with pTaG2 and pT2G3 with CIS respectively, three patients had 2 localizations of CIS and finally four patients had a pT2G3 tumour. The patient without histological confirmed tumour was correctly diagnosed with all three forms of cystoscopy. The detection rate on patient level, considering the highest tumour stage or grade, in the 19 patients with tumour was 14/19 for FFC, 17/19 for RFC and 15/19 for RWLC. Of the 27 lesions 19, 23 and 20 were found with FFC, RFC and RWLC respectively. The results per tumour category are shown in Tables 1 and 2 on patient and lesion level respectively. The false positive detection rate of FBC (15%) was low in this study, and similar to that of RFC (20%) and RWLC (15%). Overall fluorescence intensity using the flexible system was evaluated to be 76% (30–147%) using the visual analogue score (VAS) as compared to the rigid blue light scope.

All patients were included in the safety analysis. Four (20%) patients reported each 1 adverse event. Two patients had hematuria and clots, one patient had hematuria before the start of the transurethral resection and during the resection one patient had a small bladder perforation. None of these adverse events was considered to be related to HAL cystoscopy, flexible of rigid. No serious adverse events were reported.

Table 1
Detection rates per patient (considering highest tumour stage or grade)

	n	FFC positive	RFC positive	RWLC positive
T0	1	0 (=correct)	0 (=correct)	0 (=correct)
TaG2	8	6	7	8
TaG3	1	1	1	1
CIS only	3	1	2	1
T1G3	1	1	1	1
T2G3	6	5	6	4
Total	19	14	17	15

FFC: flexible fluorescence cystoscopy; RFC: rigid fluorescence cystoscopy; RWLC: rigid white light cystoscopy.