Is there a learning curve for photodynamic diagnosis of bladder cancer with hexaminolevulinate hydrochloride?

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GRAVAS S, EFSTATHIOU K, ZACHOS I, MELEKOS MD, TZORTZIS V. Is there a learning curve for photodynamic diagnosis of bladder cancer with hexaminolevulinate hydrochloride? The Canadian Journal of Urology. 2012;19(3):6269-6273.

Introduction: *To assess the learning curve for fluorescence cystoscopy using hexaminolevulinate hydrochloride (HAL) in patients with bladder cancer.*

Material and methods: *Fifty patients underwent bladder instillation with HAL. Two senior residents inspected separately the bladder using white light cystoscopy, followed by fluorescence cystoscopy and mapped the lesions. An experienced with photodynamic diagnosis (PDD) urologist also performed both cystoscopies, mapped, resected or cold biopsied suspect lesions under the supervision of another experienced urologist. To evaluate the learning curve, patients were divided into five subgroups, including group 1 (patients 1-10), group 2 (11-20), group 3 (21-30), group 4 (31-40) and group 5 (41-50). The kappa statistics was calculated to assess interobserver agreement between the physicians and the false positive rates of urologists and residents were also compared.*

Results: *Histologically verified tumors were diagnosed in 103 of 142 lesions identified by PDD. The interobserver agreement between urologists and residents was moderate, moderate, good, excellent, and excellent for group 1, 2, 3, 4, and 5, respectively. Both residents had increased false positive rates compared to urologists in all subgroups of patients but this difference did not reach statistical significance. In addition, false positive rate of residents was declining as the number of procedures was increasing.*

Conclusions: *Our data suggest that 20 cases of HAL PDD are required to achieve a good interobserver agreement between inexperienced and experienced operator, and excellent agreement is achieved after 30 cases. The false positive rate of inexperienced operators was comparable to the experts and showed a gradual decrease.*

Key Words: hexaminolevulinate hydrochloride, photodynamic diagnosis, bladder cancer, learning curve, fluorescence cystoscopy

Introduction

During the last years, fluorescence cystoscopy has regained attention due to the development of new generation photo sensitizers, such as hexaminolevulinate hydrochloride (HAL) that offers more rapid urothelial accumulation, better fluorescence contrast and less photobleaching than previously used fluorophobes.[1] Published studies have reported that fluorescence cystoscopy with HAL significantly improves the detection rate of papillary tumors and carcinoma in situ (CIS) compared to white light cystoscopy only, resulting in more appropriate treatment for some of the patients and in lower recurrence rate.[2-9] A recent meta-analysis of

Accepted for publication February 2012

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the available studies on photodynamic diagnosis (PDD) showed that PDD detects more bladder tumor–positive patients (20%), especially more with CIS (39%), than white light cystoscopy, while PDD increases tumor-free survival significantly.[10] The European Association of Urology (EAU) guidelines on the non-muscle-invasive urothelial carcinoma of the bladder state that PDD should be restricted to those patients who are suspected of harboring a high grade tumor, particularly CIS (grade of recommendation B).[11] On the other hand, studies have reported that PDD is characterized by a rather low specificity.[2,10,12,13] One of the contributing factors could be the lack of adequate training in the use of fluorescence cystoscopy that would reasonably result in an increased number of false positive findings. However, there is no study that evaluates the learning experience of urologists in PDD. Therefore we conducted the present study to investigate and define the learning curve for fluorescence cystoscopy using hexaminolevulinate hydrochloride.

Material and methods

Patients with newly diagnosed or recurrent bladder cancer were prospectively enrolled in the study. Exclusion criteria included patients with gross hematuria, if they had a known allergy to HAL or a similar compound, and those with intravesical therapy within 3 months prior to the study. The study was approved by the Ethics Committee of our institution and was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the Declaration of Helsinki (September 10, 2004 version). Patients' permission was taken after they had read the protocol and been informed about the procedure.

Patients underwent bladder instillation with 50 mL of a 2.0 mg/mL (8 mM) solution of HAL hydrochloride in phosphate buffered saline (Hexvix) through a 12 ch catheter 1 hour prior to the transurethral resection of the known tumor. After emptying of the bladder, inspection by white light cystoscopy was performed, with a D-light system xenon arc lamp (Karl Storz) providing the light source. The number and location of all exophytic lesions and suspicious areas were precisely mapped onto a bladder chart. The bladder was then inspected by HAL fluorescence cystoscopy using a band filter on the xenon arc lamp to supply blue light (wavelength 380 nm to 450 nm). The number and location of all fluorescing lesions and suspicious areas were again mapped on the same bladder chart.

According to the study protocol, two senior residents without any supervision (blinded to each other) performed both cystoscopies sequentially and mapped the lesions. The residents were also obliged to indicate areas of false, weak fluorescence for the purpose of the analysis. The only experience of the residents with the method was a demonstration video before the initiation of the study. Afterwards, an experienced urologist (blinded to residents findings) also mapped the lesions using white light and PDD cystoscopy while in addition another experienced urologist supervised these two procedures. These qualified urologists had attended a training course on fluorescence cystoscopy at an expert center and had performed more than 30 PDD procedures prior to the study with false positive rates comparable to those reported in the literature. Transurethral resection of the tumors and/or cold cup biopsies were taken only after the all visualizations were completed to avoid biopsy induced bleeding that might jeopardize subsequent visualization and diagnosis. The decision to biopsy an area was determined by the experienced urologists. In case of disagreement between urologists, all the ambiguous areas were cold biopsied. Residents were present during cystoscopies and resections of the experienced urologist. All histology and biopsy samples were examined by pathologists blinded to whether the lesions were identified by white or blue light.

To assess the impact of the learning curve on procedure outcome patients were divided into five subgroups, including group 1 - patients 1 to 10, group 2 - 11 to 20, group 3 - 21 to 30, group 4 - 31 to 40 and group 5 - 41 to 50. The kappa statistics (k) and 95% confidence intervals were calculated to assess interobserver agreement between the physicians. The strength of agreement for a kappa value was classified using the following criteria: poor agreement, 0.00 to 0.19; fair agreement, 0.20 to 0.39; moderate agreement, 0.40 to 0.59; good agreement, 0.60 to 0.79; and excellent agreement, 0.80 to 1.00.

The definition of competence to perform the technique adequately was also evaluated in terms of false positive rate. False positive rate per lesion for the experienced urologists was defined as the number of biopsied lesions with benign histology with fluorescence cystoscopy divided by the overall number of lesions biopsied under blue light. False positive rate per lesion for residents was defined as the number of falsely detected lesions (benign proven histology or rejected by the experienced urologists) divided by the overall number of suspicious lesions seen under blue light. The clinical outcomes between the two groups were tested using the Fischer's exact test and p value less than 0.05 was considered to indicate significance.

Results

Fifty patients who underwent transurethral resection of bladder tumor (TURBT) were enrolled in the study. Thirty-one patients had newly diagnosed bladder carcinoma and 19 patients had recurrent bladder carcinoma (17 of them had underwent intravesical instillations at least 3 months prior to TURBT). The distribution of patients with recurrent bladder carcinoma and those with prior intravesical instillations in the five groups of patients (from 1 to 5) was 3, 4, 4, 3, 5 and 3, 3, 3, 3, 5, respectively. Demographic data of the patients are provided in Table 1. In total 142 lesions identified under blue light were resected or cold biopsied and histological examination of biopsied lesions confirmed the existence of 103 transitional cell carcinomas. Therefore the overall false positive rate for PDD was 27.5%. From the remaining 39 lesions, 8 were classified as flat urothelial hyperplasia and 31 as normal urothelium but with the presence of inflammation in 25 cases (80.6%). Two more bladder tumors were detected only by white light cystocopy resulting in a detection rate of 98.1% (103 out of 105) for HAL PDD with 13 malignant lesions to be found only by blue light cystoscopy. The detection rate of white light cystoscopy was 87.6% (92 out of 105).

The kappa values of interobserver agreement between the experienced urologists and resident 1 for interpreting lesions under blue light was 0.489 (moderate agreement), 0.524 (moderate agreement), 0.664 (good agreement), 0.805 (excellent agreement) and 0.833 (excellent agreement) for the patients group 1, 2, 3, 4 and 5, respectively, Table 2. In addition, the experienced urologists and resident 2 had similar kappa values resulting in moderate (kappa 0.595) for group 1, moderate (kappa 0.573) for group 2, good (kappa 0.665) for group 3, excellent (kappa 0.833) for group 4, and excellent interobserver agreement (kappa 0.816) for group 5, Table 2. In addition the interobserver agreement between residents and urologist for the conventional white light cystoscopy was excellent for all groups of patients (data not shown).

TABLE 1. **Patient demographics**

Parameters	**n (%)**
Patients	50
Male	34 (68)
Female	16 (32)
Age, yrs	69.7 ± 10.4
Diagnosis	
Primary	31 (62)
Recurrent	19 (38)
Intravesical instillations	
Yes	17 (34)
No	33 (66)

The false positive rates per lesion of urologists were 25.8%, 27.2%, 28.0%, 26.6% and 30.4% for cases 1-10, 11-20, 21-30, 31-40 and 41-50, respectively. Both residents had increased false positive rates compared to urologists in all subgroups of patients but this difference did not reach statistical significance. In addition, false positive rate of residents was declining as the number of procedures was increasing. The difference of false positive rate per lesion between urologists and residents 1 and 2 narrowed from 15.2% to 11.3%, to 9.9%, to 6.6%, to 2.9% and from 12.0%, to 11.3%, to 9.0%, to 3.4%, to 2.9% for the five groups of patients, respectively. Detailed results are presented in Table 3. It should be underlined that resident 1 did not miss any bladder carcinoma from the 103 malignant tumors detected under blue light whereas the resident 2 missed two tumors.

Discussion

White light cystoscopy is one of the most common diagnostic procedures in a urological setting and represents one of the tasks that residents become familiar with, very early in their training period. Cystoscopy has unsurpassed sensitivity and specificity

TABLE 2. **The interobserver agreement for interpreting lesions under blue light**

	Kappa values (95% CI)				
Cases	**1-10**	**11-20**	**21-30**	**31-40**	**41-50**
Urologist vs Resident 1	0.489 (0.254-0724)	0.524 (0.295-0.753)	0.664 (0.454-0.873)	0.805 (0.643-0.966)	0.833 (0.651-1.0)
Urologist vs Resident 2	0.595 (0.377-0.813)	0.573 (0.345-0.801)	0.665 (0.453-0.876)	0.833 (0.676-0.989)	0.816 (0.676-1.0)

TABLE 3. **False positive rate per lesion of residents and urologists**

Cases	Urologists	Resident 1	δFPR1	p	Resident 2	δFPR2	p
1-10	25.8%	41.0%	15.2%	0.14	37.8%	12.0%	0.21
11-20	27.2%	38.5%	11.3%	0.23	38.5%	11.3%	0.23
21-30	28.0%	37.9%	9.9%	0.31	37.0%	9.0%	0.35
31-40	26.6%	33.3%	6.7%	0.38	30.0%	3.4%	0.50
41-50	30.4%	33.3%	2.9%	0.54	33.3%	2.9%	0.54

δFPR1 = difference in false positive rate between Resident 1 and Urologists
δFPR2 = difference in false positive rate between Resident 2 and Urologists

in detecting exophytic bladder tumors, but flat tumors and, in particular, CIS may be missed by conventional endoscopy in up to one third of the cases.[10,14] In addition, white light cystoscopy, remains an operator-dependent technique and a considerable numbers of false positives are also seen with white light cystoscopy.[15] For new invasive procedures or approaches like PDD with which there is limited or no experience during training, the transfer of technology and surgical aptitude is problematic requiring the performance of multiple procedures to gain experience.[16] For these reason, definition of learning curve is necessary to conclude competence with the procedure. To our knowledge, the present study is the first that evaluates the learning curve of fluorescence cystoscopy using hexaminolevulinate hydrochloride. Our results indicate that after 20 cases, an inexperienced with the method physician achieves a good agreement with an experienced one. The agreement between the experienced and inexperienced urologist for interpreting lesions under blue light rises to excellent after 30 cases.

One of the weaknesses of photodynamic diagnosis is its high false positive rate with up to a third of fluorescent areas on PDD being histologically benign. Comparative studies have reported that false positive rate with HAL cystoscopy ranged from 11% to 39% on biopsy level whereas the corresponding rate for white light cystoscopy varied from 9% to 31%.[10] False-positive fluorescence may be induced by the lack of operator experience with PDD, inflammation or scarring after previous TURB, recent intravesical therapy or the presence of simple hyperplasias.[12,13,15,17] In line with these findings, the false positive rate of urologists was higher in group 5 likely due to the higher number of patients with recurrent tumors and prior instillations, although the overall number is small for further analysis between the groups. Like white light cystoscopy, PDD is an operator-dependent technique and false positive rate may also reflect the operator attitude to this method. In a multi-center study, analysis of the false positive rates by institution indicated that some investigators may have been more aggressive in taking biopsies of any mucosal abnormality.[6] The uncertainty and the lack of confidence of inexperienced physicians in the interpretation of fluorescence areas may also result in increased number of biopsies. In our study, both residents had higher false positive rates compared to urologists in all subgroups of patients but this difference did not reach statistical significance. In addition, as the number of performed cases increased, this gap was closing from 15.2% to 2.9% and from 12.0% to 2.9% for residents 1 and 2, respectively, Table 3. The overall false positive rate of experienced urologists was 27.5% with an additional bladder carcinoma detection rate of 12.4%.

It has been reported that the main factor of error for trainees is the fluorescent appearance of tangentially viewed mucosa because of the nonspecific accumulation of protoporphyrin IX (PPIX) in normal urothelium. This is more possible to occur when investigating the bladder neck, trigone, or diverticula.[18] Direct illumination in front of the lesion by holding the endoscope perpendicular and closer to the bladder wall is recommended to eliminate false fluorescence.[2] A fully distended bladder wall will also reduce the risk of false positives resulting from tangential illumination of the mucosal folds.[19] In an attempt to reduce the number of false-positive results of suspect PDD-positive flat lesions, Bordiet et al investigated five endoscopic criteria.[20] It was found that only a slightly raised appearance and detachment of fluorescence by gentle stroking with the loop (pink veil sign) were associated with the diagnosis of CIS. Trainees should be aware of these pitfalls, and tips and tricks of the procedure in order to shorten and simplify the learning curve of PDD.

The intensive study of videocassettes after each holmium laser enucleation of the prostate operation during the learning period and discussion of critical steps with an expert resulted in improvement of the quality of the procedure performed by a novice.[21] Video recording of PDD and review of the suspect lesions in comparison with the histological outcome might contribute to a further decrease of false positive results and consequently of the learning curve but this remains to be proven.

The main limitation of the study is that only suspect lesions indicated by the qualified urologists were biopsied. There is always the theoretical risk to miss some malignant lesions correctly identified by the residents and misinterpreted by the urologists. To eliminate this potential risk all lesions indicated by the residents should have been resected but this was considered to be unethical for the patients. It could be also argued that during the learning curve only patients with newly diagnosed bladder cancer should be evaluated in order to allow trainees to be familiar with the procedure and decrease the risk of a higher false positive rate due to the presence of scarring and inflammation from previous resections and instillations. However, our decision was to include both patients with new or recurrent bladder carcinoma since the potential increased false positive rate would apply to both experienced and inexperienced physicians and would be unlikely to significantly affect the outcome. Therefore the population of the present study represents patients we treat in our daily practice.

Conclusions

Our experience showed that while training is required in the use of PDD, it is a relatively straightforward, well standardized and reproducible procedure. In the current series, 20 cases of HAL PDD are required to achieve a good interobserver agreement between inexperienced and experienced operator, and excellent agreement is achieved after 30 cases. In addition, our data showed a gradual decrease in false positive rate that was comparable to that of experts.

Disclosure

No competing financial interests exist □

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