Repeated applications of impression cytology to increase sensitivity for diagnosis of conjunctival intraepithelial neoplasia

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Accepted 20 March 2011
Published Online First 15 April 2011

ABSTRACT

Purpose To increase sensitivity of impression cytology (IC) for the diagnosis of conjunctival intraepithelial neoplasia (CIN) by three repeated applications of IC.

Methods This study included 35 eyes with a clinical diagnosis of CIN and 6 eyes with pinguecula as control. All eyes received IC by three consecutive applications of the cellulose acetate filter paper. All eyes in the CIN group had subsequent surgical excision with histopathological evaluation. The sensitivity of each application of IC for the diagnosis of CIN was determined.

Results In the control group, all IC specimens were negative for CIN. In the CIN group, with positive histopathology in all cases, the first IC was positive in 17 eyes (56.7%), showed atypical squamous cells indefinite for dysplasia (ASCID) in 8 (26.7%) and was negative in 5 (16.6%). The second application was positive in 25 eyes (83.3%), showed ASCID in 3 (10%) and was negative in 2 (6.7%). The third application was positive in 26 eyes (87.7%), showed ASCID in 3 (10%) and was negative in 1 (3.3%). The second application resulted in a statistically significant higher positive yield than the first application ($p=0.009$), with no significant difference between the second and the third applications ($p=0.12$).

Conclusion Consecutive repeated applications of filter paper significantly increased the diagnostic sensitivity of IC for the diagnosis of CIN.

Conjunctival intraepithelial neoplasia (CIN) refers to a dysplastic change of the epithelium which does not invade the underlying basement membrane.[1] Histopathologically, the lesion is considered as 'mild CIN' with partial-thickness involvement of the epithelium or as 'severe CIN' with epithelial full-thickness involvement. Clinically, CIN appears as a fleshy, sessile, nodular or thin lesion usually at the limbus in the interpalpebral fissure and less commonly in the palpebral or forniceal conjunctiva. This lesion can also be keratinised with a leukoplakic appearance.[2] Numerous risk factors have been described for CIN including exposure to ultraviolet light,[3–5] infection with human papilloma virus[6–8] or HIV[9–11] and exposure to chemical agents.[12]

Although the clinical appearance of the lesion may be suggestive of CIN, tissue biopsy is necessary to confirm the diagnosis. Because many patients with primary or recurrent CIN can now be treated with topical chemotherapy without surgical excision of the lesion,[13–15] impression cytology (IC) has recently been used to confirm the diagnosis without the necessity of performing histological evaluation of the excisional biopsy. IC is a simple technique for removing one to three superficial layers of the epithelium by applying collecting devices, either cellulose acetate filter papers or Biopore membrane device (Millipore Corp., Bedford, Massachusetts, USA).[16] This technique of cytology has been used for the diagnosis of various ocular surface diseases.[16] Although IC has a high sensitivity of 70%–82% for the diagnosis of ocular surface squamous neoplasia, including CIN and squamous cell carcinoma (SCC),[17–20] there are still cases in which IC yields false negative results. The keratotic surface of the lesion or the presence of dysplastic cells deep within the epithelium may be the reason for these false negative results.[16 21]

In IC, it has been shown that multiple applications of the collecting papers to the same area may result in access to deeper parts of the normal epithelium.[16 22] Therefore, in this study we hypothesised that three consecutive applications of the collecting filter paper to the surface of CIN by approaching the deeper epithelium may result in higher sensitivity of the technique to confirm the diagnosis.

METHODS

This prospective controlled study included 35 eyes of 34 patients with clinically diagnosed CIN lesions who were scheduled to undergo excisional biopsy as the study group and also 6 eyes of 6 patients with clinically benign conjunctival lesions as the control group. None of the patients in either group had received any topical chemotherapy or any surgical procedure prior to IC. The protocol for this study was approved by the Institutional Review Board of Farabi Eye Hospital, Tehran, Iran.

All patients received complete ocular examination including measurement of best-corrected visual acuity and intraocular pressure, slit lamp biomicroscopy and photography, and staining with fluorescein and Rose Bengal. The advantages and disadvantages of using IC were thoroughly discussed with the patients and all had consented to have the test.

All included lesions in both the study group and the control group received three consecutive tests of IC by the same person. IC test was performed with some modifications from a method previously described.[23] In brief, cellulose acetate filter papers (Sartorius AG, Goettingen, Germany) with a pore size of 0.2 μm were cut into 6×3 mm pieces with

one square end and one pointed end to track the orientation of application. After instillation of 0.5% tetracaine hydrochloride eye-drops as a topical anaesthetic and wiping away the excessive tear fluid, the cellulose acetate paper was gently pressed on the lesion for about 5 s. The paper was then peeled off and immediately put in a fixative solution that was composed of 20% ethanol, 37% formaldehyde and glacial acetic acid with a volume proportion of 20:1:1, respectively. Application of the paper was repeated three times consecutively, and the order of the applications was recorded.

All IC specimens were stained with Gill's modified Papanicolaou staining method and were evaluated by a single pathologist (MM). The pathologist was masked to the clinical diagnosis of each patient and also to the order of sampling by filter papers. The surface area of the filter paper which had been covered by epithelial cells was first determined. For this, whole-image reconstruction was performed using photographs taken at low magnification (40×) followed by analysis of the digital image by Adobe Photoshop; samples with less than 10% of the coverage were discarded.

The following cytological criteria were used to diagnose CIN[21]: nuclear enlargement more than two times the dimensions of the nucleus of normal conjunctival cells (when measured along their longest axis), irregular nuclear contour, coarsely clumped chromatin, nuclear pleomorphism, binucleation or multinucleation, presence of nucleoli and nuclear or cytoplasmic vacuolisation. If the above characteristics were present in most cells, the specimen was considered to be positive for CIN. When nuclear enlargement was less than twice the dimensions in normal conjunctival cells, or when it was limited to only few squamous cells, the specimen was categorised as atypical squamous cells indefinite for dysplasia (ASCID). If none of the above characteristics was positive, the specimen was regarded as negative for CIN (figure 1).

Within 1 month after performing IC, all patients with clinically diagnosed CIN lesions (35 eyes) subsequently underwent surgery with excisional biopsy of the conjunctival lesions, and the specimens were sent for histopathological examination by the same pathologist who was masked to the results of clinical diagnosis and IC. The patients in the control group (six eyes) did not receive any surgical procedure.

Statistical analysis was performed using SPSS version 15. χ^2 and ANOVA tests were used to compare different applications of IC regarding the positive yield and the mean surface area of the filter paper covered by the epithelial cells, respectively. p Values of 0.05 or less were considered as statistically significant.

RESULTS

Five eyes of five patients with CIN had inadequate IC samples and so were excluded from the study. Therefore, the study group comprised 30 eyes with clinically diagnosed primary CIN in 29 patients (20 men and 9 women) with a mean age of 65.7±13.1 years (range, 38–82 years) (table 1). All CIN lesions were located in the limbal region with various degrees of conjunctival and corneal involvement. Histopathological evaluation of the excisional biopsy confirmed the diagnosis of CIN in all cases with none showing evidence of invasive SCC. The control group consisted of six eyes of six patients (4 men and 2 women) with a mean age of 62.5±5.9 years (range, 57–73 years). All eyes in the control group had the clinical diagnosis of pinguecula.

IC was performed in all cases without any complication. In the control group, all IC specimens were negative for CIN and there was no evidence of dysplasia at any (table 1). Cytological findings in this group included variable degrees of squamous metaplasia with no significant cytological difference between three consecutive samples.

The results of three consecutive applications of IC in the CIN group are shown in table 1 and figure 2. The first IC was positive in 17 eyes (56.7%), showed ASCID in 8 (26.7%) and was negative in 5 (16.6%). The second application was positive in 25 eyes (83.3%), showed ASCID in 3 (10%) and was negative in 2 (6.7%). The third application was positive in 26 eyes (87.7%), showed ASCID in 3 (10%) and was negative in 1 (3.3%). The

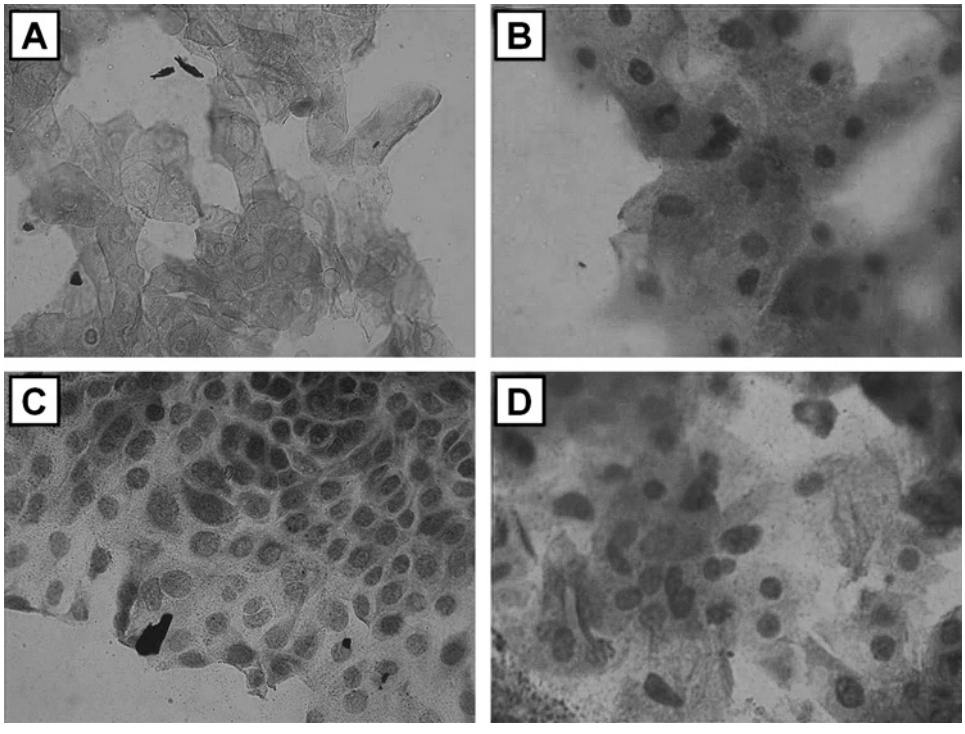

Figure 1 Different cytological patterns in impression cytology of eyes with conjunctival intraepithelial neoplasia (CIN) (Gill's modified Papanicolaou staining, 650×): (A) Negative for CIN; (B) atypical squamous cells indefinite for dysplasia; (C) positive for CIN in a non-keratinising dysplasia; (D) positive for CIN in a keratinising dysplasia.

Table 1 Results of three consecutive applications of impression cytology in eyes with CIN and the control group

Eye no.	Age (years)	Results of impression cytology: First application	Second application	Third application	Histopathological diagnosis
CIN group					
1	70	Positive	Positive	Positive	CIN
2	76	Positive	Positive	Positive	CIN
3	41	Positive	Positive	Positive	CIN
4	81	Positive	Positive	Positive	CIN
5*	82 (OD)	Positive	Positive	Positive	CIN
6*	82 (OS)	Positive	Positive	Positive	CIN
7	78	ASCID	ASCID	Positive	CIN
8	64	Positive	Positive	Positive	CIN
9	75	Positive	Positive	ASCID	CIN
10	38	Negative	ASCID	Positive	CIN
11	62	Positive	Positive	Positive	CIN
12	52	Negative	Positive	Positive	CIN
13	68	Positive	Positive	Positive	CIN
14	78	ASCID	Positive	Positive	CIN
15	43	Positive	Positive	Positive	CIN
16	79	Positive	Positive	Positive	CIN
17	76	ASCID	Positive	Positive	CIN
18	80	Positive	Positive	Positive	CIN
19	63	Positive	Positive	Positive	CIN
20	76	ASCID	Positive	Positive	CIN
21	42	Negative	Negative	Positive	CIN
22	58	Negative	Negative	Negative	CIN
23	55	Positive	Positive	ASCID	CIN
24	72	ASCID	ASCID	ASCID	CIN
25	64	Positive	Positive	Positive	CIN
26	69	Positive	Positive	Positive	CIN
27	63	ASCID	Positive	Positive	CIN
28	59	Negative	Positive	Positive	CIN
29	61	ASCID	Positive	Positive	CIN
30	79	ASCID	Positive	Positive	CIN
Control group					
31	73	Negative	Negative	Negative	N/A
32	65	Negative	Negative	Negative	N/A
33	62	Negative	Negative	Negative	N/A
34	58	Negative	Negative	Negative	N/A
35	60	Negative	Negative	Negative	N/A
36	57	Negative	Negative	Negative	N/A

Demographic data, except for the patient's age, have been omitted to comply with patient anonymisation.
*Right and left eyes of the same patient.
ASCID, atypical squamous cells indefinite for dysplasia; CIN, conjunctival intraepithelial neoplasia; N/A, not available; OD, right eye; OS, left eye.

second application resulted in a statistically significant higher positive yield than the first application (p=0.009). However, the difference in positive results between the second and the third applications was not statistically significant (p=0.12).

In 15 eyes (50%), all applications were positive; in one eye (3.3%), all specimens were revealed to be negative; in one other eye (3.3%), all samples showed ASCID. In seven eyes (23.3%) with ASCID at the first application, the test became positive at the second application in six eyes (20%) or at the third application in one eye (3.3%). Four eyes (13.3%) with negative results at the first application showed positive results at the second application in two eyes (6.7%) or at the third application in two other eyes (6.7%). In two eyes (6.7%) with positive results at the first and second applications, the test showed ASCID at the third application.

The correlation of IC and histopathological findings showed that in cases with positive specimens in all IC applications

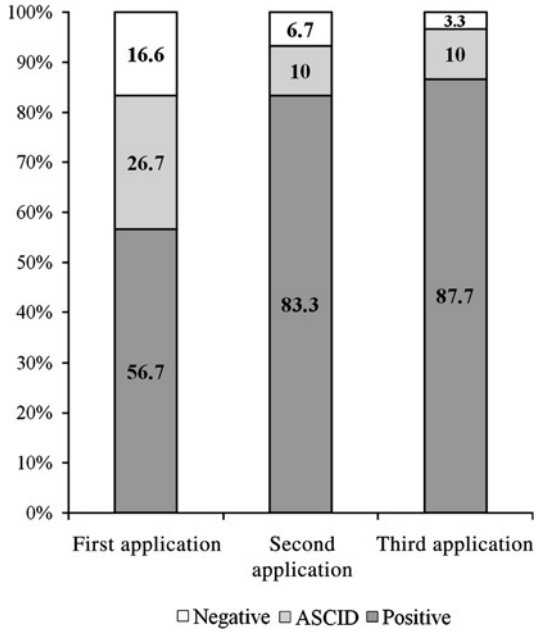

Figure 2 Results of three consecutive applications of impression cytology in eyes with conjunctival intraepithelial neoplasia. Results have been shown as the percentage of positive, atypical squamous cells indefinite for dysplasia (ASCID) or negative specimens in each application of impression cytology.

(15 eyes) there was full-thickness involvement of the epithelium with features of keratinising dysplasia, non-keratinising dysplasia or syncytial-like clustering. In one eye with the ASCID pattern in all specimens, histopathology revealed keratinising dysplasia with mild nuclear changes involving full thickness of the epithelium. In another eye with negative test in all specimens, there was keratinising dysplasia with marked hyperkeratosis and parakeratosis and mild to moderate nuclear changes, limited to the deeper third of the epithelium (mild CIN). Furthermore, in eyes with initially negative or ASCID pattern and subsequent positive test in further applications (11 eyes), 9 showed keratinisation with variable degrees of nuclear changes, 1 showed a non-keratinising dysplasia with moderate nuclear atypia and in another eye there were features of syncytial-like clustering.

Table 2 shows the mean surface area of the filter paper covered by the epithelial cells at the different applications for both the CIN group and the control group. In the CIN group, the area covered by the epithelial cells decreased progressively at the second and the third applications and the differences were statistically significant (p=0.001). In the control group, although the area covered decreased at the second and third ICs compared with the first application, the differences were not statistically significant (p=0.09). There was no statistically significant difference in the extent of the area covered by the epithelial cells between the CIN group and the control group.

Table 2 Percentage of the filter paper covered by the epithelium in three consecutive applications of impression cytology in eyes with conjunctival intraepithelial neoplasia (CIN) and in the control group

	Percentage of the filter paper covered by the epithelium: First application (%)	Second application (%)	Third application (%)	p Value
CIN group	67.7±19.8	52.0±19.1	38.3±17.6	0.001
Control group	63.3±42.5	48.3±32.5	36.7±30.5	0.09

DISCUSSION

This study shows that in patients with histopathologically proven CIN, repeated applications of the filter papers used in IC resulted in significantly higher positive results. For the diagnosis of CIN, the second and third applications of IC were significantly more sensitive than the first application. Although the difference in sensitivity between the second and the third applications was not statistically significant, it does not make this difference as clinically insignificant for the diagnosis of CIN. This higher sensitivity of IC obviates the necessity of excisional biopsy for patients in whom topical chemotherapy can be contemplated instead of surgical excision.

In this study, the first application of IC by filter paper in patients with CIN resulted in 56.7% positive results and 83.4% total positive and ASCID results. This is comparable with previous studies of IC in patients with ocular surface squamous neoplasia including CIN and SCC. Nolan *et al* reported positive results in 78% of eyes with ocular surface squamous neoplasia, with an accuracy of 80% and 70% in eyes with CIN and SCC, respectively.[18] Using the Biopore membrane instead of cellulose acetate filter papers, Tole *et al* reported a positive result of 80% in 25 eyes including 24 with CIN and 1 with SCC.[19] Compared with histopathological findings, Tananuvat *et al* showed positive and negative accuracy rates of 97.4% and 52.9%, respectively, for IC in eyes with ocular surface neoplasia.[20] Although the positive yield with the conventional method is high, there are still cases in which the result of IC is false negative.

In an attempt to increase the accuracy of the IC, in this study three consecutive applications of the filter papers were used to reach the deep epithelium. Interestingly, it was found that subsequent applications resulted in significantly higher positive results (figure 2). The second application increased the positive results to 83.3%, which is 26.6% higher than that of the first application. Moreover, the total positive and ASCID results increased to 93.3%, which is 9.9% higher than that for the first application. Although the third application resulted in a higher yield than the second application, the difference was not significant. There were 87.7% positive results and 97.7% total positive and ASCID results in the third application, which were only 4.4% higher than those for the second application. It is noteworthy that in five eyes with initially negative results, IC was able to detect CIN in two eyes (40%) with the second application and in two other eyes (40%) with the third application. Similarly, in eight eyes with ASCID results, which were not definitive for CIN, definitive criteria for the diagnosis were met in six eyes (75%) and one eye (12.5%) with the second and the third applications, respectively.

Histopathologically, dysplastic changes in CIN may involve various thicknesses of the epithelium, starting from the basal layer outwards.[24] Involvement of the superficial layers is seen in higher grades of histopathological severity. Therefore, in cases with milder involvement, there may be more false negative results with IC which removes only one to three superficial layers of the epithelium. For example, Tananuvat and colleagues observed negative results in 2 (66.7%) out of 3 eyes with mild CIN and only in 3 (16.7%) out of 18 eyes with moderate or severe CIN.[20]

In this study, consecutive repeated applications of the filter paper resulted in significantly higher sensitivity due to access to deeper epithelium. Previously, Singh and coworkers were able to show the morphology of the normal basal limbal epithelium by repeated applications of IC filter papers in cadaveric eyes.[16] In addition, Barros *et al* used two consecutive applications of IC in eyes with ocular surface epithelial lesions.[22] Although they accessed the deeper cells by repeating the application, they did not compare the accuracy of the first and the second applications to detect the abnormal cells.

In contrast to cervical CIN lesions which are usually non-keratinising, ocular CIN lesions are often of a keratinising type. Keratinising CIN lesions may result in a false negative IC test due to the small number of cells present in the IC sample.[16 22] In our study, only in one eye, all three consecutive IC samples were false negative. This eye had a low-grade keratinising dysplasia with considerable hyperkeratosis and parakeratosis. Eleven out of 14 other cases which showed false negative results or ASCID in any of 3 consecutive samples also had keratinising dysplasia. Therefore, totally 12 out of 15 eyes with at least 1 false negative result or ASCID in any of 3 consecutive samples had keratinising dysplasia. It seems that keratinisation leads to more false negative results at first application and repeated sampling in this population of CIN cases is more likely to result in subsequent positive IC. Further studies are required to demonstrate the results of repeated applications of IC in eyes with different histopathological features of ocular surface neoplasia.

In our study, no attempt was made to correlate the results of repeated applications with the clinical features of CIN. However, Gill's modified Papanicolaou staining method was used in this study which is preferable to other stains such as Giemsa and haematoxylin/eosin to diagnose keratinising CIN.[25] Future research is necessary to determine the optimal IC technique in eyes with keratinising CIN.

The surface area of the filter paper covered by the epithelial cells decreased significantly at the second and third applications compared with the first application, in both the study group and the control group (table 2). While the first application had a mean coverage of 67.3±21.6% in both the CIN group and the control group, the area covered decreased to 51.7±19.9% and 38.2±18.4% at the second and third applications of IC, respectively. It seems that deeper epithelial cells are more tightly bound to each other, leaving fewer cells to be removed by IC. In this study, possibly due to a significant decrease in the covered surface of filter papers, two eyes in the CIN group, which had positive results at the first and second applications, showed ASCID at the third application. The best technique for removing deeper epithelial cells remains to be elucidated.

Although false positive results in IC have previously been reported,[20] none was found in our study and in studies reported by others.[17–19] All samples in the control group, which consisted of eyes with pinguecula, showed negative results with decreasing coverage of the filter paper by epithelial cells in subsequent applications. It should be kept in mind that IC is very helpful unless the result conflicts with the clinical picture or where the actual clinical diagnosis is uncertain and the result is negative. In these doubtful cases, excisional biopsy needs to be performed for accurate diagnosis. Other limitations of IC include that it may not differentiate between CIN and invasive neoplasia[22] and its inability to reveal the surgical margins if no excision is to be performed for topical chemotherapy. In addition, to be optimally accurate, experience in IC interpretation is necessary on the part of the reporting pathologist.

Our investigation was performed as a controlled prospective study in which the pathologist was masked to the clinical diagnosis and also to the order of samples. However, the main limitations of the study were that there was no case with

invasive SCC or recurrent CIN and the small number of eyes in the control group. With these limitations in mind, it seems that repeated consecutive applications of IC will lead to significantly more sensitivity for diagnosis in eyes with CIN, thereby obviating the need for excisional biopsy. This is particularly helpful in cases which can be treated with topical chemotherapy without performing surgery. Future studies are required to unravel the optimal non-invasive test for diagnosis of CIN.

Competing interests None.

Ethics approval This study was conducted with the approval of the Eye Research Center, Farabi Eye Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

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Br J Ophthalmol 2012 96: 229-233 originally published online April 15, 2011
doi: 10.1136/bjo.2010.201103