SUMMARY AND CONCLUSION

Warts result from infection with a double-stranded DNA virus tropic to human skin. The agent responsible is HPV, of which there are more than 150 serotypes. Some are known to cause cervical cancer, but common warts that affect nongenital skin are not thought to have malignant potential.

Infection with HPV occur most commonly by direct contact with individuals who harbor clinical or subclinical HPV-associated lesions, or indirectly through contaminated surfaces and objects. Papillomaviruses are resistant to heat and desiccation due to the absence of a viral envelope and even laser fumes may contain infectious virions.

There is currently no specific antiviral therapy available to cure HPV infection. Existing modalities mostly aim at the destruction or removal of visible lesions or induction of cytotoxicity against infected cells. Treatment options for warts include mechanical destruction and adjustment of the patient's immune system through medications, and observation. The most commonly employed treatments involve destroying the affected tissue by freezing, burning, curetting (usually with electrodesiccation), or applying topical acids and chemotherapeutics may sometimes be used in refractory or severe cases.

Intralesional bleomycin therapy has been used in the treatment of warts since the 1970s but, although an effective method of treatment
for resistant warts, it is still not widely used because of pain associated with the injection.

Given its toxic nature as a chemotherapeutic agent and the increased incidence of adverse effects, treatment of common warts with bleomycin has been limited to cases that do not respond to conventional therapies. Intrallesional bleomycin may induce local toxic side effects like local urticaria, local Raynaud's phenomenon, lymphangitis or nail changes such as shedding, onychodystrophy and onycholysis. The possibility of using bleomycin as a first-line agent have been raised because of the relatively simple procedure and increased patient satisfaction when compared with destructive modalities such as electrocautery.

This study was done to evaluate the efficacy and safety of intrallesional bleomycin in the treatment of cutaneous warts, and to determine its effect on the wart and the skin by histological and immunohistochemical methods.

This study was carried out on patients complaining of different types of warts (n=105), they were selected from patients attending the Dermatology and Andrology clinic, Benha University Hospital. They were classified into the following groups.

Group A included 50 patients complaining of warts which have been injected intrallesionally by bleomycin and have been followed up clinically for clearance of warts or recurrence. Patients were complaining of warts of different types (common, plane, filiform, periungual, palmar and plantar). Pregnant patients and those
complaining of Raynaud's phenomenon or vascular diseases were excluded.

Patients were subjected to physical examination in the first visit to document type of warts, number, site, size of each and duration. Bleomycin was injected intralesionally into warts by conventional tuberculin syringe. Patients were injected by bleomycin every two weeks for three sessions. If the warts persist after three injections, the treatment was considered a failure. All patients were followed up for any recurrence for the next six months after clearance of their warts.

Twenty five patients (group B) complaining of warts were injected intralesionally by normal saline and this group was considered as a control for group A. Patients were injected by the same type of syringe, the same amount, and the same technique as in group A. These patients were followed up after two weeks in order to record any change of their warts.

Group C included 30 patients with common or plantar warts. All warts were not treated before by any other modalities. They were injected intralesionally by bleomycin and they were biopsied for histological and immunohistochemical examination. The biopsies were taken before bleomycin injection and after 2, 3, 4, 5, 7 and 15 days of bleomycin injection.

Six healthy volunteers (group D) were selected for intradermal bleomycin injection. They neither have warts nor received bleomycin injection before. Bleomycin was injected into the ventral
surface of the forearm and the site of injection was biopsied for histological and immunohistochemical study.

After 3 injection sessions plantar, palmar, and common warts showed a total cure rate of 98%, 93%, and 93.5% respectively. On the other hand periungual, filiform, and plane warts showed a total cure rate of 100%. The total cure rate was 97% (140 out of 145 warts). The therapeutic response was not affected by patient's age, sex, disease duration or being treated before by any treatment modality. The majority of patients perceived mild to moderate pain after bleomycin injection. None of them develop any other local toxic side effects like local urticaria, Raynaud's phenomenon, lymphangitis or nail changes such as shedding, onychodystrophy and onycholysis.

After bleomycin injection, almost all wart biopsies showed histopathological changes in the form of keratinocyte necrosis, hemorrhage, and neutrophilic infiltrate. These changes begin to appear in warts after 2 days of injection. First, the changes involved no more than one third of epidermal thickness. After 5 days, these changes involved two thirds of wart thickness. After 7 days of bleomycin injection, these changes involved all wart thickness. After 15 days of bleomycin injection, all wart biopsies showed massive hemorrhage, severe neutrophilic infiltrate and liquefactive necrosis of keratinocytes.

All wart biopsies including the control were subjected to IHC stain to detect CD44 expression. The stain was exclusively
membranous in all biopsies including the control. The control group showed complete staining of all thickness of the epidermis. After bleomycin injection, wart biopsies showed gradual loss of IHC stain according to duration of injection. The loss of IHC stain was noted in upper third of wart thickness first. By time, the loss of IHC stain extended to involve the whole wart thickness.

Normal skin biopsies after 3 days of bleomycin injection showed keratinocyte necrosis and hemorrhagic infiltrate by H&E stain. These changes were seen mainly in upper portion of the epidermis.

IHC stain was exclusively membranous in all normal skin biopsies before and after bleomycin injection. Before bleomycin injection, biopsies showed complete staining of all epidermal thickness. After 3 days of bleomycin injection, skin biopsies showed loss of IHC stain by variable degrees but most of them showed loss of the stain from upper third of epidermis.

The results of group C&D showed that histopathological changes were gradual by time and were consistent with loss of IHC stain. The histopathological changes and IHC changes appeared first in upper portion of wart growth and these changes spread by time to involve the whole wart thickness. Hemorrhagic necrosis was the main feature in both groups which affect the upper portion of epidermis before the basal one.

In conclusion, intralesional bleomycin is a very effective and well tolerated first line therapy in the treatment of all types of cutaneous warts regardless of patient's age, sex, disease duration or
being treated before by any modalities. The loss of expression of CD44 was not different in warts and normal skin. This loss of CD44 expression may be attributed to hemorrhagic necrosis of keratinocytes after bleomycin injection. The appearance of hemorrhagic necrosis and its increase by time is most probably the primary effect of bleomycin.