Vol. 16, No. 4.
December, 1975.

THE RESPONSE OF HUMAN TENDON TO HYDROCORTISONE INJECTION

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SYNOPSIS

For the purpose of determining the effects of hydrocortisone on human tendons, the calcaneal tendons of fifteen patients going for lower limb amputation were infiltrated with a suspension of hydrocortisone acetate in lignocaine. At varying intervals after the injections, the amputations were performed and the calcaneal tendons were immediately removed from the limbs and formalin-fixed. As controls, another three patients were given normal saline injections into their tendons. Histological examination of the tendons of the test patients showed necrosis of collagen followed by repair. These changes provided possible explanations for ruptures of tendons after local injections of hydrocortisone which are being increasingly reported in the literature.

INTRODUCTION

Rupture of tendons has been increasingly encountered in patients following local infiltration of hydrocortisone. There is some clinical evidence that hydrocortisone is at least partially responsible for such ruptures (Sweetnam, 1969). However, animal experiments to study the effects of hydrocortisone on tendon and tendon healing have produced conflicting results. Using rabbits, Berkin (1955) showed that cortisone did not significantly interfere with tendon union, as judged by histological features and tests of tensile strength. On the other hand, Wrean, Goldner and Markee (1954) found that cortisone definitely weakened tendons in dogs and lowered the breaking points of sutured tendons.

Microscopical changes in tendons following injection of hydrocortisone into them have been observed in controlled studies in rabbits (Balasubramaniam and Prathap, 1972; Bedi and Ellis, 1970) but similar investigations in human subjects have not been documented.

Because of possible differences in response to hydrocortisone by tissues of dissimilar animal species, a study was undertaken to record the local effects of hydrocortisone on human tendons.

This paper describes the histological changes in human tendons at varying time intervals after local infiltration of hydrocortisone and discusses the relationship of hydrocortisone injections to tendon rupture.

MATERIAL AND METHOD

Eighteen patients who required lower limb amputations for various reasons were selected for the study which covered a three-year period. Twelve of the patients had to have their lower limbs removed for diabetic gangrene, five for malignant tumours, and one for 'useless limb'. In patients with diabetic gangrene, only those whose inflammation did not extend proximal to midfoot were used in the study.

The calcaneal tendons of fifteen patients were injected with one millilitre of a suspension containing 25 milligrammes of hydrocortisone acetate and two millilitres of 1% lignocaine, the usual combination employed in clinical practice. Amputations were performed at varying intervals of approximately 3 hours, 24 hours, 72 hours, 1 week and 2 weeks after the injections had been given (Table I). As controls, the calcaneal tendons of three patients were infiltrated with preparations comprising one millilitre of normal saline and two millilitres of 1% lignocaine.

Immediately after a lower limb had been amputated, the calcaneal tendon containing the site of hydrocortisone injection was carefully dissected out and preserved in formol

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TABLE I

THE NUMBER OF AMPUTATED LIMBS EXAMINED AT EACH TIME INTERVAL AFTER HYDROCORTISONE INJECTIONS

Time Lapse	Number of AMPUTATED LIMBS	
	Hydrocort Inj.	Controls
3 hours	2	0
24 hours	5	1
48 hours	4	2
72 hours	2	0
1 week	1	0
2 weeks	1	0
TOTAL	15	3

saline. After paraffinembedding, histological sections of the tissues were cut at 5-micron thickness and stained with Haematoxylin & Eosin and Masson's trichome stain. Microscopic examination was performed under both ordinary and polarised light.

RESULTS

At 3 hours: At the site of injection, the collagen fibres were disorganised, with loss of the normal parallel arrangement of the fibres and separation of adjacent fibres by irregular vacuoles. The degenerating fibres were pale-staining and were no longer birefringent. There was a total absence of inflammatory cell response (Fig. 1).

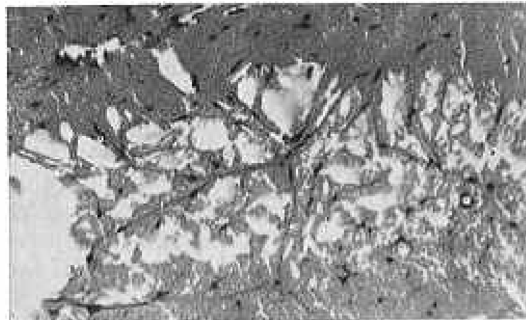

Fig. 1. Degenerating collagen fibres are separated from each other by vacuoles. At 3 hours. (H. & E. × 600)

At 24 hours: Inflammatory cells, which were mainly polymorphonuclear in type, had arrived at the site of injection. These were accompanied by a few erythrocytes and some foamy histiocytes. As the necrotic collagen was being removed by the scavenger histiocytes, fibroblastic repair was already beginning (Fig. 2).

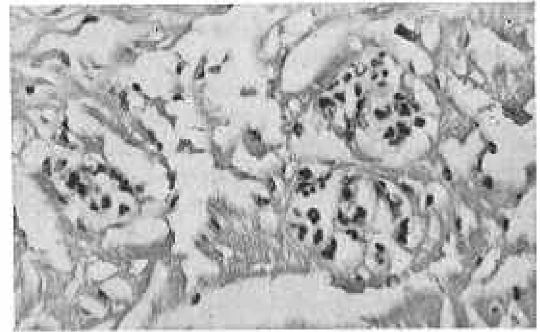

Fig. 2. Polymorphonuclear leucocytes at the injection site. At 24 hours. (H. & E. × 600)

At 48 hours: Attempts at repairing the breach were prominent, with profuse proliferation of fibroblasts in which some mitoses were noted. By this time, the polymorphonuclear leucocytes had disappeared and had been replaced by occasional lymphocytes (Fig. 3).

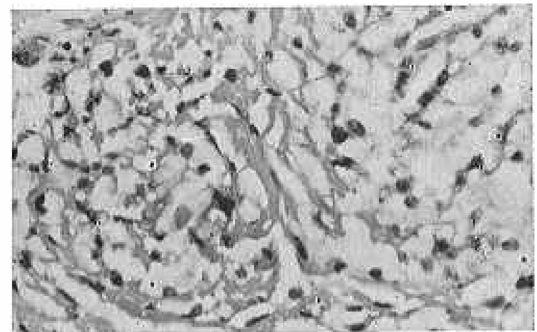

Fig. 3. Proliferation of fibroblasts and infiltration by lymphocytes. At 48 hours. (H. & E. × 600)

At 72 hours: The completion of the process of repair was indicated by the replacement of fibroblasts by histologically mature collagen. There was shrinking of the fibroblastic nuclei and inflammatory cells were absent. However, the newly-formed collagen did not exhibit the birefringence shown by normal collagen fibres (Fig. 4).

Fig. 4. Newly-formed collagen in the centre showing loss of birefringence. At 72 hours. Polarised light. (H. & E. × 600)

At 1 week and 2 weeks: There was puckering of the collagen tissue at the site of injection. Although the collagen in the scar tissue resembled the surrounding normal collagen under ordinary light microscopy, it lacked the birefringent property of the latter (Fig. 5). The changes noted at 1 week and 2 weeks were essentially the same.

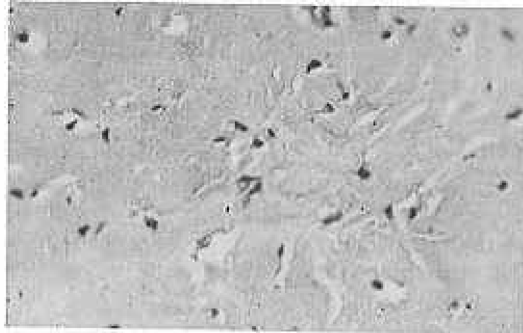

Fig. 5. Newly-formed collagen which looks normal under non-polarised light. At 1 week. (H. & E. × 600)

Controls: One calcaneal tendon removed 24 hours after injection with normal saline showed an acute inflammatory infiltrate at the site of injection, without evidence of vacuolar degeneration of the collagen fibres (Fig. 6). Two tendons removed 48 hours after injection appeared normal histologically at the sites of injection; no inflammatory cells were present. In all three instances, there was preservation of the birefringent property of the collagen.

Fig. 6. Mild inflammatory infiltration without real damage to collagen tissue. Control at 24 hours. (H. & E. × 600)

Examination for underlying disease: Histological examination of sections prepared from tendon tissue at a non-injected site showed that the tendon was normal in every case; there was no evidence of the disease process for which the amputation was performed.

DISCUSSION

In a study of the present nature, objections to the validity of the observations may be raised because of possible interference of the results by the primary pathological conditions in the patients' limbs. These doubts can be readily dispelled because the histological sections of the tendons at some distance away from the sites of injection showed no evidence of pathology and there was certainly no demonstrable effect resulting from the patients' underlying diseases. Furthermore, the microscopic changes at the sites of hydrocortisone injection were found to be the same in cases which shared the same time lapses between injection and amputation.

The results show that hydrocortisone has a definite damaging local effect on human tendons. While the control cases showed no tendon damage apart from a mild infiltration of inflammatory cells which had disappeared after forty-eight hours, the tendons infiltrated with hydrocortisone underwent necrosis with subsequent reparative changes. Even after two weeks, there was absence of birefringence of the replaced collagen indicating that a complete return to normalcy had not been achieved.

When the present observations were compared with those of Balasubramaniam and Prathap (1972) who carried out their experiment on rabbits, there was a marked difference in response shown by the two species investigated. While the onset of inflammatory reaction in the tendon was the same in both species, the processes of further destruction and eventual repair were spread over much longer periods in rabbit than in man. Repair, as indicated by the laying down of new collagen tissue, was brought about in four weeks or more in rabbit tendons, while it required three days to complete in human tendons. This difference in response might not be entirely due to species variation, as the dose injected into human tendons in term of milligrammes of hydrocortisone acetate per kilogramme of bodyweight was approximately one-third of that injected into the rabbit tendons.

In the pathogenesis of tendon rupture following hydrocortisone injection, many suggestions have been put forward. At present, the most widely favoured ones are (1) damage to the tendon due to the physical presence of the injected suspension (Balasubramaniam and Prathap, 1972), (2) direct chemical effect of

hydrocortisone which not only initiates the inflammatory response but also, by interfering with the maturation of fibrous tissue, delays the healing of the tendon (Bedi and Ellis, 1970) and (3) enzyme-mediated destruction due to the release of a protease by hydrocortisone (Woessner, 1968).

In clinical practice, ruptures of tendons usually follow repeated local injections of hydrocortisone. The damage caused by a single injection in a relatively large tendon like the human calcaneal tendon may not significantly alter the tensile strength of the tendon; however, cumulative damage due to repeated injections may weaken the tendon to a critical point beyond which it ruptures. Rarely, a small tendon ruptures after a single injection of hydrocortisone. The authors have come across a patient whose extensor pollicis longus tendon ruptured on the fourth day following local infiltration of 25 milligrammes of hydrocortisone acetate in lognocaine for De Quervain's tenovaginitis.

The present study shows clearly that hydrocortisone has a definite deleterious local effect on human tendons. Care must always be taken when using local injections to treat De Quervain's tenovaginitis, tendo-achilles tendinitis or trigger fingers, that the hydrocortisone suspension is not given directly into the tendons. In order to avoid any damage to neighbouring tendons, multiple injections, even at intervals, should be discouraged. It is often the multiplicity of injections into a site that is the cause of tendon rupture in clinical practice.

REFERENCES

1. Balasubramaniam, P. and Prathap, K.: "The effect of injection of hydrocortisone into rabbit calcaneal tendons." J. Bone and Joint Surg.., 54-B, 729-734, 1972.
2. Bedi, S.S. and Ellis, W.: "Spontaneous rupture of the calcaneal tendon in rheumatoid arthritis after local steroid injection." Annals of Rheumatic Diseases, 29, 494-495, 1970.
3. Berkin, C.R.: "Effects of cortisone on the healing of tendons in rabbits." Royal Society of Medicine Proceedings, 48, 610-613, 1955.
4. Salter, R.B. and Murray, D.: "Effects of hydrocortisone on musculo-skeletal tissues." J. Bone and Joint Surg., 51-B, 195, 1969.
5. Sweetnam, R.: "Corticosteroid arthropathy and tendon rupture." J. Bone and Joint Surg., 51-B, 397-398, 1969.
6. Woessner, J.F. Jr.: "Biological mechanisms of collagen resorption." In 'Treatise on Collagen' Vol. 2, 'Biology of Collagen' part B, p. 301. Edited by B.S. Gould., London and New York: Academic Press, 1968.
7. Wrean, R.N., Goldner, J.L. and Markee, J.L.: "An experimental study of the effect of cortisone on the healing process and tensile strength of tendons." J. Bone and Joint Surg., 36-A, 588-601, 1954.