The Egyptian Experience in the Use of Colchicine In Lumbar Disc Disease

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Abstract. One hundred patients with severe and resistant manifestations of lumbar disc prolapse formed the clinical material of this study. Their ages ranged between 26 and 58 years with an average of 38.7 years, and the range of the follow-up period was 8 months to 5.5 years with the mean average of 3 years and 8 months. All the patients were subjected to different measures of conservative treatment of lumbar disc disease including bed rest, smoking prohibition, nonsteroidal anti-inflammatory drug (NSAID) and muscle relaxant administration, epidural steroid injections, and physiotherapy. All of them had resisted such conservative management, and had become candidates for surgical interference. Candidates of this study were divided into two equal groups (50 patients in each) in a randomized double-blind fashion. Patients of the first group received intravenous injections of 1 mg colchicine in a 2 ml volume twice weekly for 3 consecutive weeks, while those of the placebo group were injected with the same volume and number of sterile saline solution. They were evaluated by a blinded assistant. Neither the patient nor the evaluating assistant had been informed about the contents of the injections in order to comply with the requirements of the randomized double-blind study. About 87% showed excellent improvement without the need for surgical interference. The only complication was due to extravasation of colchicine that caused colchicine burn and phlebitis.

Introduction

Colchicine is derived from the seeds and corns of the plant Colchicum autumnale also known as meadow saffron or as autumn crocus. The plant is a member of the lily family, however, and is not a true crocus. Colchicine was listed in the Ebers Papyrus, an Egyptian document of about 1550 BC, as a saffron [1]. The first clearly recorded use of extracts of the plant dates to the sixth century AD, when Alexander of Tralles recommended it. It was said that he gave colchicine to his soldiers to enhance their health and their fighting abilities [2].

The drug was reintroduced into therapy by Nicholas Husson, a French army officer, in Eau Medicinale d’Husson, a patent medicine that he offered as a panacea for innumerable diseases in 1780. The nature of the active ingredient was shown by Want in 1814 to be colchicine [3,4]. Pelletier and Caventose [5] determined that the active principle of colchicine was the alkaloid colchicine, and then produced a pure preparation. The purified substance has been in constant use in the treatment of acute gout ever since.

Over the past three decades Michael Rask had discovered that colchicine is therapeutic for disc disease (and for other related resistantly painful spinal disorders) [6–10]. He also stated that there is something truly specific about colchicine that brings about healing of these resistantly painful spinal disorders.

Herniated disc disease of the human spine is for the most part, a benign, self-limiting painful disorder for which surgery (and other drastic invasive procedures such as chemonucleolysis) probably are not the treatment of choice [11]. He also recorded that, it seems clear after having treated over 1500 patients with unsuccessful spinal surgery, that surgery of human disc should never be done for pain alone.

Colchicine is man’s most powerful and safe anti-inflammatory drug [11]. To show its safety, it was used to treat patients who have severe cirrhosis of the liver (in the end-stages of liver disease)—to bring about healing of their damaged livers [12]. Colchicine has been proven to extend the lives of the liver-damaged patients [13].

Colchicine has been proven effective in disc disease [14] in a double-blind study of two equal groups of patients with severe disc disease using intravenous colchicine in one group and intravenous saline as a placebo in the other.

Since then, the Food and Drug Administration (FDA) has considered colchicine effective in disc disease, and it was listed under the index number of 21,807 [14].

Prof. Xiao, Yu Mu [15] of Shantung Medical University, Shantung China, proved that oral colchicine is effective in disc disease in his large double-blind study where a large group of disc-suffering patients were
treated with oral colchicine (1 mg per day for 14 days) and another similar group with Indocin (indomethacin 75 mg/day for 14 days). Patients who took colchicine had a 61.9% rate of excellent or good results, while only 16.7% of the indomethacin group had excellent or good results. Also, side effects in the colchicine treated group were much less than those in the indomethacin-treated patients [15].

The aim of this study is to assess and report the Egyptian experience of colchicine’s effectiveness in a double-blind randomized study for severely resistant lumbar disc disease.

Materials and Methods

Two equal groups of fifty patients with severe and resistant symptoms and signs of lumbar disc disease, participated in this study. Their ages ranged between 26 and 58 years with an average of 38.7 years. Follow-up periods ranged from 8 months to 5.5 years, with an average of 3 years and 8 months. Each patient was assessed with particular reference to symptoms, signs, and functional disability. The symptoms of which the patient complained are summarized in Table 1. The most common presenting symptoms were low backache and pain in the leg, which was defined as pain extending beyond the knee [16]. This was present in 97% of the patients, although 72% of them also had lower backache alone. A history of claudication was reported by 13% of the patients.

The signs are summarized in Table 2. The most common neurological abnormality was a motor deficit, which was present in nearly half of the patients. Straight leg raising was significantly reduced in 47%; on the other hand, muscle spasm in the paraspinal muscles that reduced spinal movement was the most common sign, in 85% of the patients.

Routine hematological (especially hemoglobin percentage, red and white cell counts, and biochemical investigations including S. uric acid kidney and liver function) and urine examinations were conducted. All the patients were radiographically investigated using plain radiography in all, myelography in 36%, and CAT scanning in 64%. Electromyographic studies were not carried out as a routine during the period of this review, and only

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<th>Table 1. Symptoms in 100 patients with lumbar disc disease</th>
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<td>Symptoms</td>
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<tr>
<td>Low back and leg pain</td>
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<tr>
<td>Low backache</td>
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<td>Leg pain</td>
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<td>Numbness and or paraesthesia radiating thigh-calf-foot</td>
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<tr>
<td>Weakness of the leg(s)</td>
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<td>Claudication</td>
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2 patients, at the end of the period reviewed, had this investigation.

All the patients had received conservative treatment that included analgesia (NSAID), bed rest, physiotherapy, manipulations, spinal support, and epidural steroid injections before they were referred to this study. Also, all the patients were advised to stop smoking. The majority of smokers (37 of 62 smokers, or 59.6%) were able to stop smoking. Of those who stopped smoking, 18 patients were in the placebo group and 19 in the group treated with intravenous (IV) colchicine. All of the patients in this study were candidates for surgical interference with fenistration or laminectomy together with discectomy.

Candidates of this study were divided equally into two groups in a randomized fashion. Patients in one group received an intravenous injection of 2 ml containing 1 mg colchicine twice weekly for 3 weeks. Patients in the other group were injected with the same volume and number of injections of sterile saline solution as a placebo. They were evaluated by an assistant resident who was not included in this study. Neither the assistant nor the patients were informed of the contents of the injection. The assistant just asked each patient to quantitate the percentage improvement of symptoms. We decided not to evaluate our patients personally and asked an assistant who was not aware of the contents of the intravenous injections at the time to ensure the requirements of the randomized, double-blind study.

Evaluation was started on the second day of the first injection, after 3 weeks, and monthly for 6 months, at least some patients were followed up until the end of 5.5 years. Assessment was performed either subjectively (the sense of pain, either low backache or sciatica), or objectively by measuring the degree of straight leg raising, back muscle spasm and muscle weakness of the ankle, toes, or calf. Some cases were examined by CAT scanning (21%—12% of them with previous CAT scan and 9% with previous myelography).

Results

Pain

Subjective evaluation of the sense of pain (either low back pain or sciatica or both) was performed by asking
the patient to describe his or her level of pain. This was conducted by another doctor, who did not know the contents of the injection that the patient had received. Evaluation was performed on the second postinjection day and was continued for the following 3 weeks. From the second day there was a great reduction in pain sensation in the group injected with intravenous colchicine. This drop of pain sensation was continued until the end of the third week to reach a minimum with an average of 88.6%. At the same time in the placebo group, there was an improvement by only 5.3% (Table 3).

**Muscle Weakness**

Three weeks after the beginning of the therapy, patients were subjected to a program of physiotherapy to strengthen the back, thigh, leg, and ankle muscles. Eight of 10 patients (80%) in the colchicine-injected group showed progressive improvement of muscle weakness, but those of the placebo group showed no improvement (Table 4).

**Straight Leg Raising**

Forty-seven out of 100 patients showed severe limitation in the straight leg raising test with positive Lassue sign. Twenty-seven were in the colchicine-treated group, while the rest (20 patients) were in the placebo group.

As with pain, there was an immediate and progressive improvement in the colchicine-treated group in regards to leg raising limitation, as 25 patients (92.6%) were able to passively raise their extended legs without pain. On the other hand, the placebo group showed no improvement, but even at the end of the third week, there was some increased numbers in the limited straight leg raising test (Table 4).

**Muscle Spasm**

Eighty-five percent of both groups showed spasm of the paraspinal muscles with limitation of the spinal movements in one or more directions. Thirty-nine of the 45 patients (86.6%) showed relaxation of those previously spasmotic muscles from the second day of the colchicine injection until the end of the third week, while those patients in the placebo group showed no improvement, and even these had shown an increased number of patients with spasmotic lumbar muscles (Table 4). By calculating the average of the four categories (pain, muscle spasm, muscle weakness, and straight leg raising) we get an improvement with colchicine intravenous injection of 86-95%.

All the patients were subjected to many important laboratory investigations including liver and kidney function tests, full urine analysis, and full blood count (red and white cell and platelet counts). All these investigations were repeated every 6 months to be compared with the previous ones until the end of the follow-up period, but no patient had any change in the results of their laboratory tests.

**Complications**

The only real complications from the use of intravenous colchicine are the problems of extravasation during intravenous delivery that may cause colchicine burn (it occurred in 4% of cases in this series) or due to colchicine irritation of the vascular intima that may result in delayed colchicine phlebitis (1% rate in our study). These two complications can be entirely avoided.

Colchicine burn can be treated by stopping the injection immediately and injection of the burn site by marcaine 0.5% mixed with triamcinolone acetonide, together with the application of local ointments of Benadryl cream and lidocaine 4%. On the other hand, IV colchicine phlebitis can be treated by IV injection of the affected vein with 1 cc of lidocaine mixed with 0.5 cc betamethasone phosphate along with 5 cc normal saline [17].

**Discussion and Conclusion**

In this study, 100 patients with a well-diagnosed resistant lumbar disc disease with severe sciatia were collected

| Table 3: The effect of colchicine in different kinds of pain in lumbar disc disease |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Patients with problem | Improved | %IMP* |
| Colchicine group                | Placebo group      |
| Lower back pain                 | 49                | 46              | 93.8            | 48              | 2                | 4.2              |
| and sciatica                    | 39                | 34              | 87.1            | 33              | 0                | 0.0              |
| Sciatica                        | 27                | 23              | 85.1            | 31              | 2                | 6.5              |
| Average                         |                    |                 | 88.6            |                 |                  | 5.35             |

* IMP = improvement.
Table 4. The effect of colchicine on muscle weakness, straight leg raising, and muscle spasm

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<th>Colchicine group</th>
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<td>Patients with</td>
<td>Improved</td>
<td>%</td>
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<tr>
<td>Muscle weakness</td>
<td>10</td>
<td>8</td>
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<tr>
<td>Straight leg raising</td>
<td>45</td>
<td>39</td>
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<td>Muscle spasm</td>
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and treated in a randomized, double-blind fasion with intravenous colchicine in the first group and intravenous saline in the other group. All of these patients were candidates for surgical intervention. The colchicine-treated group showed an improvement of the symptoms and signs at a rate of 86.95%.

Colchicine was shown to be effective in lumbar disc disease. What is the mechanism of action for such successful function? Rask in 1989 [11] summarized these actions in a valuable explaining points:

1. *Anti-inflammatory*. Colchicine is the most powerful and oldest known anti-inflammatory medication [10]. It seems to act directly on discal inflammation, and tends to “deinflame” the inflamed spinal nerve roots. Colchicine’s effectiveness in disc disease can be immediate in the patient with severe discal back pain and sciatica, as it can miraculously work in patients who have acute severe gouty arthritis. Also, patients who have suffered intense, unrelievable back and limb pain—over a long period of time—will sometimes permanently respond to only one intravenous injection of colchicine [10].

2. *Washes out painful crystalline deposits*. Most damaged discs and surrounding tissue have accumulated a certain amount of crystalline depository elements (e.g., gouty or calcium pyrophosphate dehydrate). These crystalline substances are exceedingly painful and irritating foci of inflammation. Colchicine is most effectual in bringing immediate dissolution and deinflammation of these deposits, thus allowing the patient instantaneous pain relief [18].

3. *Increases endorphin-producing neurons*. Besides its powerful anti-inflammatory activity, it is known that colchicine causes the growth of endorphin-producing neurons in the spinal cord, thus increasing patients’ resistance to their painful discs. (Surg. Pract. News, 1981).

4. *Combats the atopic elements of the disc syndrome*. It is also known that one of colchicine’s actions is its anti-allergenic effect. There is a certain amount of atopia in the disc disease syndrome [19], and colchicine is quite efficacious in countering it.

5. *Inhibits amyloid deposits in the disc*. Amyloid deposits have been found in the herniated disc [20]. Colchicine is an effective medication for preventing the deposition of amyloid in patients with rheumatoid arthritis or Mediterranean fever [21]. Rask [10] also demonstrates that colchicine can prevent or ameliorate painful amyloid deposits in the damaged disc.

6. *It shrinks the disc*. Meek [22] showed through spinal lumbosacral CAT scan before and after colchicine treatment that colchicine has a disc-shrinking ability. He followed up the patient with CAT scan 3 months following intravenous and oral colchicine therapy and found that there was complete resolution of the patient’s ruptured disc, severe back and leg pain, and muscle spasm, along with the return of limb sensation and return of the patient’s previously absent left ankle jerk deep tendon reflex. Also, he proved that due to shrinking of the prolapsed intervertebral disc, the spinal nerve root has returned to its normal configuration.

7. *It inhibits white blood cell chemotaxis*. Malawista has presented strong arguments to suggest that colchicine’s mechanism of action in the treatment of acute gout is essentially the same as in mitosis arrest—an action on microtubule precursors. He demonstrated the presence of microtubules in polymorphonuclear leukocytes (PNL) and that these microtubules were sensitive to colchicine. Malawista has described the sensitivity of many polymorphonuclear functions to colchicine in vitro, although generally at concentrations much higher than those achievable in vivo during therapy. The only functions of PNL consistently inhibited by colchicine in concentrations achievable in vivo were those concerned with the generation of, or response to, a chemotactic stimulus. Because the PNL is necessary for acute urate crystal-induced inflammation, it has generally been assumed that colchicine acts on this cell.

In this study, we got improved results (a rate of 86.95%) although lower than those of other authors such as the average successful results of Rask (the discoverer of colchicine’s effectiveness in lumbar disc disease) which were about 98.2%.

The reasons for failure of therapy of the patients in this series could be due to discontinuation of the drug administration because of the development of the painful
phlebalgia and colchicine burn in some patients, and also may be due to discontinuation of tobacco smoking. Tobacco and alcohol (and other dependency-producing substances) interfere with colchicine effectiveness in patients who suffer disc disease [10]. Smoking cuts down oxygenation and circulation to the intervertebral disc [23]. Also, the use of tobacco drastically reduces the body’s own production of endorphins (the natural pain-relieving polypeptides) [24]. In a very large series of patients, Enrick and Rask [25] found that conservative therapy for disc disease is more likely to fail in those who smoke. Additionally, those patients who use tobacco and alcohol are more likely to have spinal surgery (or other invasive spinal procedures) [25]. Also, patients who smoke tobacco are more likely to have unsuccessful back surgery and/or chemonucleolysis [26,27]. That is why we stress cessation of smoking in conservative treatment of patients with lumbar disc disease.

From the results, we surmise that pain starts to disappear on the second day after intravenous colchicine administration in disc disease patients, while numbness is the very last symptom to disappear. Deep tendon reflexes commonly reappear, sometimes within a few days, after the onset of colchicine therapy, but muscle weakness must be worked to get complete recovery.

The laboratory studies of the patients were compared every 6 months until the end of the follow-up period. There were no changes to liver and kidney function tests or white cell, red cell, and platelet counts; hence there were no liver, kidney, nor bone marrow affections. But Rask [10], after following up his 6000 patients for over 35 years of use of colchicine (intravenously or orally), he reported, “... in thousands of patients whom I have treated with disc disease and arthritis, I have never once seen an abnormal laboratory test as a result of a patient’s use of colchicine, but I have seen some abnormal liver tests as a result of the other oral nonsteroidal anti-inflammatory medication.”

Low white blood cell (WBC) counts are known to occur in Boecks, Sarcoid, lupus erythematosis, and in patients with prolonged and severe rheumatoid arthritis. Colchicine helps these patients maintain higher WBC counts by decreasing the activity of their disease. Colchicine has had absolutely no adverse effect on the hematological system of any of the thousands of patients that Rask had treated for disc problems (or other painful inflammatory disease). This is particularly true because the dosage needed to cure disc trouble (or to ameliorate rheumatoid or other arthritic disorder) is minimal [10].

The reason colchicine is so safe is due to its side effects. The patient knows when he gets a little too much of it. He develops a touch of diarrhea, or he gets some cramping sensation in the small muscles of the hands and/or feet. By not taking one or two doses of colchicine for a day or 2, these symptoms disappear. Colchicine is a marvelous medication because its side effects are easily reversed, merely by stopping the medication [28].

The real safety of the use of colchicine appears from its marked effectiveness of oral colchicine in the treatment of patients with severe liver cirrhosis [13]. Their patients with severe cirrhosis of the liver who took oral colchicine had a mortality rate less than half of those who were not given colchicine (21% versus 47%). Also, these colchicine-treated patients had other laboratory test markers that showed significant improvement in their cirrhosis (compared to the non-colchicine treated group). The first reports of colchicine effectiveness in cirrhosis of the liver were by Kershonobich in 1979, [12] who reported good results with colchicine in cirrhosis in a double-blind, randomized trial.

The same group in long-term follow up in 1988 [29] reported “the overall survival in the colchicine group.” The 5-year survival rates were 75% in the colchicine group and 34% in the placebo group.

It has been claimed that colchicine treatment will result in genetic side effects. This hypothesis may be true if large toxic doses were used in the treatment. The recommended amount of colchicine is 1.2–1.8 mg per day, which is equivalent to 0.02 mg/kg body weight per day in a 70-kg man. This is an infinitesimally small amount compared to the dosage overload required in genetic experiments (5 mg/kg body weight) [30].

References

10. Rask MR. Colchicine use in 6000 patients with disc disease & other related resistantly-painful spinal disorders" J.