

Tuberculosis of spine: Research evidence to treatment guidelines

Anil K Jain

The named oration gives us an opportunity to remember a person who has contributed immensely toward the growth of science to serve the society. Induces introspection among orator and listeners to rededicate to the cause of suffering humanity and stimulates the future generation to perform against all odds. Kini memorial oration is delivered by immediate Past President of Indian Orthopedic Association to acknowledge the contribution of Prof. MG Kini toward science and society.

Dr. Mangalore Gopal Kini was born in 1893 at Mangalore and completed his medical education from Madras Medical College in 1918.¹ He joined Indian Army in 1919 and was awarded Military Cross for exemplary gallantry services. He later attained FRCS and MCh from Liverpool. He first worked in General Hospital and later joined King George's Hospital at Visakhapatnam as Professor of Operative Surgery. He joined as medical superintendent at Stanley Medical College until he retired in 1948. He was very much ahead of time as far as his vision and mission for health care in India are concerned. He was a firm believer of that for the improvement in patient care we have to strengthen postgraduate training program and the research and publication. He himself had 98 publications in various national and international journals. The government of India designated him as examiner to various universities and as a chief of inspecting board of Indian Medical Council. Postretirement he worked for up

gradation of Armed Forces Medical College (Pune) and founding father of specialty hospital for Children Hospital at Haji Ali, Bombay. He was a very keen player of cricket. He passed away on August 22, 1952, at the age of 59 due to a heart attack. This write up is dedicated to Prof. MG Kini, a genius diligent master of skills and who gave his heart and soul to fraternity to provide pain relief to suffering humanity.

EVOLUTION OF MEDICINE

The practice of medicine is an art which has transformed from an art based on belief in supernatural force to an art based on science. This art was developed by talented physicians over many centuries by their observations and its use in clinical practice (patient care). Further, this art was propagated among future generations by teacher disciple lineage (Guru Shishyaparampara). Now this art is gradually changing and developing from mere observations to documented evidence which continued to be validated.

The practice of medicine is described as “artistic application of science.” To affect a cure, the clinician has to understand the pathological process occurring in humans body, the response of the body to control it and has to add therapy (deciding the size and duration of therapy is an art) to affect a cure. As more and more knowledge for diagnosis, treatment and prevention of disease will be based on scientific research, it will reduce the guesswork to achieve the effective patient outcome.

The medicine was started 3000 years ago in different parts of the world as modern medicine (allopathic) in Europe, Ayurveda in the Indian subcontinent and Chinese medicine.

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Access this article online

Quick Response Code:



Website:
www.ijoonline.com

DOI:
 10.4103/0019-5413.173518

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How to cite this article: Jain AK. Tuberculosis of spine: Research evidence to treatment guidelines. *Indian J Orthop* 2016;50:3-9.

The Ayurveda was based on a combination of empirical treatments and erroneous religious and philosophical assumptions. It evolved from an ongoing body of practical medical experiences which passed down orally through numerous generations until eventually it was written down as “Sushruta Samhita” and Charak Samhita in the 6th century BC. Charak Samhita discussed surgical techniques of making incisions, probing, foreign body extractions, alkali and thermal cauterizations, tooth extractions, cesaerian section, and other surgical procedures.² Thus, Ayurveda was far ahead of Western medicine in surgery.

Modern medicine like Ayurveda also evolved from a long prescientific stage of development. Over the years, they applied proper scientific principles and discarded all those old ideas which were simply superstitious with no genuine medical foundation. The scientific evolution of Ayurveda did not take place. On comparing the Ayurveda and modern medicine, we find that the Western medicine has advanced while Ayurveda remained in its original prescientific stage. As a result, over the centuries now, medicine is synonymous with modern medicine while rests of them are alternative medicine.

The growth of science depends on longitudinal scientific evidence generated over a similar consecutive problems solved in a similar manner. The identification of clinical problems and their causes is of paramount importance to plan the strategy to solve. The solution is appraised on scientific parameters then the evidence is generated. The generated evidence in identical problem treated in the same way in a series of the patient becomes definitive evidence. The generated evidence if published in peer-reviewed journals allows it to be retrieved beyond human life and available worldwide and proves a foundation stone for future research.

SPINAL TUBERCULOSIS

Tuberculosis (TB) has lived in symbiosis with human beings since time immemorial and is as old as humankind. It has been demonstrated in the remains of Iron Age and Egyptian Mummies. As we have evolved in medical science, the goals of treatment have changed. In the preantibiotic era, the TB spine patients were treated by high protein diet, rest, fresh air, and sunshine in sanatorium hoping for natural quiescence of the disease. Most of the patients used to die while others remained crippled. With the introduction of antibiotics and effective anti-tubercular drugs, the tubercular lesion achieved healed status, predictably outcome improved. As a result, the goal of treatment changed to healing of lesion with residual kyphosis. Over last few decades, the life expectancy has increased and these patients started

reporting with complications of sequelae of spinal deformity and neural complications. In the present time with the improvement in diagnostics, imaging, surgical interventions and instrumentations, the objective of treatment is to “heal the lesion with near normal spine.”³

STATE OF KNOWLEDGE ON TUBERCULOSIS SPINE IN 1988

All the patients with TB spine with no neural deficit used to heal with residual kyphosis. There was a lack of consensus on what is the best method to treat TB spine. The diagnosis of spinal TB was on X-rays, hence at the time of diagnosis the lesions used to be in advance stage. The conservative and surgical options were used interchangeably. The optimum duration of treatment was unresolved between 6 months, 9 months, 12-18 months or more based on evidence of clinicoradiological healing. The instrumentations were performed by few surgeons without any specific objective. TB spine with neural complications also used to heal with the residual neural deficit and the prognostication of neural recovery could not be done.

Induction to tuberculosis spine

We confronted a case of TB spine that was treated for tuberculous paraplegia 20 years ago by anterolateral decompression. The patient had recovered neurologically. He reported back after 20 years with increasing neural deficit. Clinicoradiologically, it was an old healed TB spine with late onset paraplegia. The magnetic resonance imaging (MRI) scan was performed (a new modality for Indians 1988) to identify the cause of neural deficit. It showed as after healed vertebral lesion with severe kyphosis, acute internal salient with cord atrophy, and syringomyelia. Two other similar patients of late onset paraplegia also showed severe cord atrophy. Hence, severe cord atrophy and syringomyelia were attributed as the causes of late onset of paraplegia.⁴ These 2 cases ignited the field of exploring MRI observations in TB spine and two new research questions emerged.

- Could we diagnose spinal TB well before deformity and paraplegia as MRI picks up inflammation very early? What are the MRI correlates for the diagnosis of spinal TB and healing?
- Define the correlation of clinical course with MRI observations in the tuberculous spine with neurological complications?

DIAGNOSTIC FEATURES OF TUBERCULOSIS SPINE ON MAGNETIC RESONANCE IMAGING

Forty-nine consecutive patients with TB spine diagnosed clinicoradiologically and/or using histology/fine needle

aspiration cytology/bacteriology/molecular diagnosis (polymerase chain reaction) were evaluated by MRI for diagnostic criteria for TB spine and healing changes at the end of the treatment.⁵ The mean vertebral body (VB) involvement on X-rays was 2.61 ($n = 128$ VB) and on MRI 3.2 ($n = 161$ VB); thus lesions were more extensive on MRI than that seen on X-rays. A combination of paravertebral collection, marrow edema, subligamentous and epidural extension, contiguous VB involvement, relative preservation of disc space, epidural involvement (canal encroachment), intraosseous abscess and septate paravertebral shadows were considered diagnostic features of spinal TB on MRI. The resolution of marrow edema and collection, fatty replacement of bone marrow and resolution of cord signal intensity were observed in a healing disease. All the patients of suspected tubercular lesion which do not show classical findings on MRI should be considered as a case of diagnostic dilemma and tissue should be procured to establish tissue diagnosis before starting the treatment.

CORRELATION OF CLINICAL COURSE WITH MAGNETIC RESONANCE IMAGING OBSERVATIONS IN TUBERCULOUS MYELOPATHY

Sixty patients of TB spine with neural complications were serially followed up while on treatment by MRI and 143 MRI scans were evaluated.⁶ The observations were:

- Liquid compression, which is observed as low signal intensity on T1-weighted images (T1-WI) and bright signal on T2-WI
- Dry compression, which is mixed extradural collection with the heterogeneous signal in T1-WI and T2-WI.

The spinal cord showed: (i) Cord edema as diffuse hyperintensity in T2-WI and hypointensity on T1-WI and; (ii) myelomalacia as patchy hyperintensity in T2-WI and hypointensity in T1-WI; (iii) cord atrophy was observed as a reduction in cord volume; and (iv) syringomyelia as dilatation of the central canal.

The patients who showed gross neural recovery were labeled as “Responders” which had predominantly liquid compression, preserved spinal cord volume and cord edema. Any patient with TB of the spine with paraplegia and not having any imaging features of instability (like pan vertebral disease) are likely to show good neural outcome on treatment (nonoperative or surgical).

The patients who did not show appreciable neural recovery were described as “nonresponders group” had mixed extradural compression (dry lesion) and thick dura-arachnoid complex with disease tissue encircling the spinal cord with features of myelomalacia. Such patients

are likely to show poor neural recovery, hence, should be taken up for early surgical decompression.

IMPACT OF CANAL ENCROACHMENT ON NEURAL COMPLICATIONS

The patients showed cord compression on computed tomography (CT)/MRI and did not have clinical neural deficit were evaluated for clinical and imaging correlation. MRI/CT scan of 16 active cases of TB spine with no neural complications were enrolled.⁷ The area of the spinal cord and the spinal canal were calculated at the level of maximum compression. Up to 76% canal encroachment was found compatible with intact neural state provided no other cause of neural complication such as instability (pathological subluxation/dislocation) or vascular cause, exists.⁷ The explanation suggested was that the cord compression in the tubercular spine is gradual, hence the spinal cord adapts to this slowly developing cord compression. The neural complications may develop at lesser canal compromised if there is an evidence/element of spinal instability. Hence, the cases with MRI/CT-based cord compression should only be taken up for surgical decompression on clinical indications.

This study was the forerunner for a new clinical research question. Can we prevent the development of spinal deformity and paraplegia? In TB spine by the time radiological findings appear on X-rays it is almost 3–4 months in the pathogenesis of disease. During these 3–4 months, the patient is symptomatic and efforts should be made to diagnose the spinal tubercular lesion in the early stage of disease using imaging techniques. The clinical or clinicoradiological criteria to suspect spinal TB lesion in early stage of disease needs to be defined.

The patient with persistent localized back pain (3 months or more) with or without tenderness or spasm, with or without constitutional symptoms, with or without early radiological finding should be labeled as “observational spine” in the endemic zone for TB and need to be serially evaluated by X-rays. With subtle X-rays findings, the patient should be subjected to MRI. These X-ray findings of early suspicion will be variable depending on segment of spine affected.^{8,9}

Cervical spine: The inflammatory exudate collects in the loose areolar tissue present in front of the VB and behind trachea (prevertebral soft tissue space [PVSTS]) when the underlying VB is affected by TB. The increase in the size of this space could be the earliest radiological finding before the destruction of underlying bone is appreciated on plain X-rays. The normal size of this space is described in millimeters, but it may be variable depending on height and built of the patient. Hence, we calculated the normal PVSTS on lateral view

radiograph of the cervical spine in 300 subjects and described the space in relation to the width of the underlying VB. Before the bifurcation of nasopharynx into esophagus and trachea it, the PVSTS is one third and after the bifurcation it is two third of the width of VB behind. In front of C7, it is always less than C6. In front of the upper dorsal spine it should be 8–10 mm away from the vertebra and should follow the contour of upper dorsal spine, i.e. concave anteriorly.¹⁰ Any localized or generalized increase in PVSTS an indirect indicator of pathology in underlying bones. On such findings the underlying bone should be subjected to MRI to make a diagnosis in the underlying bone. Below D4–D5 the intervertebral disc height can be very well-appreciated on plain X-rays.^{10,11} The disc height on plain X-ray at any level should be equal or more than the disc above except D12–L1 and L5–S1. Keeping the findings in mind, the underlying disease can be suspected and diagnosed in inflammatory stage of disease well before a spinal deformity develops. The patients treated in inflammatory stage would heal with almost near normal spine.

SPINAL DEFORMITY

In countries with fewer resources these patients generally present for the first time with spinal (kyphotic) deformity. The spinal deformity either remains same or increase while on treatment. These deformities if left as sequelae, add to the risk of development of late onset paraplegia (paraplegia with healed disease). The late onset paraplegia is more often seen with healed kyphosis of 60° or more. The surgical correction of these kyphotic deformities is challenging and fraught with complications. Hence, any kyphosis in adults and children which heal with 60° or more should be surgically corrected in active disease. The final kyphosis can be predicted in adults before the start of treatment in active disease. Rajasekran *et al.* proposed a formula.¹² We analyzed 70 patients who were treated nonoperatively ($n = 40$) or by surgical decompression uninstrumented ($n = 30$).¹³ The final kyphosis recorded was correlated with initial VB height loss. It was observed that the prediction of final kyphosis was better in nonoperative group. Any patient with initial VB loss (IVBL) of more than two will end up in a final kyphosis of 66.5° hence any patient who has IVBL of 1.5 or more in dorsal and dorsolumbar spine should be surgically treated by deformity correction.

SURGERY IN SPINAL TUBERCULOSIS

The surgery in spinal TB with paraplegia with paretic intercostals muscle with/without concomitant pulmonary disease is a complicated procedure and requires excellent spinal surgery infrastructure. In underdeveloped countries, disease burden is always more than available infrastructure

for complex spinal surgery. The surgical decompression in the dorsal spine by the transthoracic transpleural approach and extrapleural anterolateral approach was compared in a randomized controlled trial. It was observed on followup CT that by both the procedures equal quality of surgical decompression can be accomplished. An adequate anterior decompression and posterior instrumentation can be performed by the extrapleural anterolateral approach. The surgical approach was modified to “T” incision from semicircular incision of anterolateral decompression to increase the extent of exposure for instrumented stabilization.^{13,14} The use of complex transthoracic anterior decompression is now rarely indicated as surgical options in TB spine.

INSTRUMENTED STABILIZATION IN TUBERCULAR SPINE

The safety of use of metal in spinal TB as biofilm formed is very thin and Antitubercular Treatment (ATT) can still penetrate to act on mycobacterium TB. The various authors performed instrumented stabilization without defining the indications of instrumentation with the objective to prevent on treatment deterioration of kyphosis. These studies were retrospective level IV case series and type of instrumentation was confusing. A meta-analysis was performed which included all articles ($n = 124$) published from 1986 to 2006 where some instrumentations have been used. None of the studies have defined indications to instrumentation. It was left to the choice of the surgeon to use instrumentation, and even the type of implant was not standardized. Most of the surgeons have instrumented spine to reduce the postsurgical deterioration of the kyphosis.^{15,16} Hence, we described the indication of instrumentation as (i) grossly unstable or potentially unstable spine, where the VB and posterior complex, both are diseased. The spine must be surgically stabilized by instrumentation so that pathological subluxation/dislocation and the consequent severe neural deficit are prevented; (ii) long segment disease, where after surgical decompression, a long anterior bridge graft is placed. This graft needs to be protected by posterior instrumentation to prevent graft breakage/displacement and consequent progression of neural deficit/deformity. Instrumentation is a mandatory step where surgical correction of kyphotic deformity is contemplated.

SURGICAL CORRECTION OF KYPHOTIC DEFORMITY IN TUBERCULAR SPINE

Surgical correction of kyphotic deformity is a complex procedure and each case has to be evaluated and planned for the surgical approach and steps of deformity correction.

We evaluated a series of patients for kyphotic deformity correction. These patients were operated by the extrapleural anterolateral approach. The issues in kyphotic deformities of spinal TB are (a) retropulsed tissue directly compressing the spinal cord; (b) shortened vertebral column of long standing; hence, spinal cord has adjusted to shortened length of the vertebral column. The surgical steps to correct kyphotic deformity described are anterior corpectomy, posterior column shortening, instrumented posterior stabilization and anterior and posterior bone grafting (both) performed simultaneously ideally by one approach where one can access both columns of spine simultaneously. These can be performed by an extrapleural anterolateral approach with posterior Hartshill instrumentation in dorsal spine. The anterior exposure of D12 to L2 disease requires retraction of aorta and preservation of L1 and L2 nerve roots, hence, a series of patients were taken for the same procedure performed by extrapleural retroperitoneal approach for thoracolumbar lesions. However, now with posterior only approach surgical correction of spinal deformities can also be achieved.¹⁷⁻¹⁹

OPTIMUM DURATION OF ANTI-TUBERCULAR TREATMENT

The evidence on optimum duration of ATT is variable between 6 mos, 9 mos, 12 mos and 18 mos. This controversy is created due to the paucity of clear observations on the end point of treatment. Most of the articles have considered clinical, clinicoradiological and hematological criteria with no recurrence for 2 years as healed status. We took MRI-based healed status as criteria to stop ATT. We conducted a study to establish the efficacy of extended DOTS category I of chemotherapy in spinal TB taking MRI observations as healed status.¹⁸ Fifty two patients were prospectively evaluated by contrast MRI. 35.2% patients were considered attained healed status at 8 months, 60% at 12 months and 90% at 18 months. It was considered unscientific to stop ATT by fixed time schedule and we need to evaluate all spinal tubercular lesions at 8 mos and subsequently to observe MRI signs of healed status. Although this issue still requires better criteria of healed status than MRI and positron emission tomography (PET) scan could be one such modality.

FAILURE OF CONSERVATIVE TREATMENT

There is a natural resistance among mycobacterium for ATT. The vertebral lesions may fail to show resolution either due to the failure of drug treatment (drug resistance) which has to be distinguished from the paradoxical response to anti-tubercular treatment. We evaluated prospectively a series of therapeutically refractory cases of TB spine.²⁰ All

patients who did not show clinical improvement on ATT or the lesion or spinal deformity deteriorated or a new lesion appeared or wound dehiscence occur at 5 months of ATT were included. The lesions were debrided and tissue was submitted for BACTEC culture. 2 of 14 cases demonstrated drug resistance and other were treated as cases of clinical drug resistance. All patients showed healing of lesion on contrast MRI/PET scan. This clinical condition needs further clinical research to define protocol for therapeutically refractory cases.

Atypical spinal TB including granulomatous disease present with unique diagnostic challenges hence are likely to be diagnosed with sequelae. The intramedullary granuloma respond/resolve with supervised ATT while extradural granulomas require surgical decompression and peeling of granulomas. Extradural granuloma generally shows good neural recovery. One third of patients with spinal tumor syndrome turns out to be intraspinal tubercular granuloma in endemic zone for TB.²¹⁻²³

During this process we reported pseudoaneurysm of aorta²⁴ and written review articles highlighting the consensus achieved and listing unanswered questions in TB spine of adults and children^{25,26} and invited to be the Guest Editor for a symposium on "Management of spinal TB" in Clinical Orthopedics and Related Research.²⁷

We could resolve on clinicoradiological predictors to suspect spinal TB and diagnose spinal TB early in the predestructive stage and prevent the development of spinal deformity and neural complication. We could provide MRI correlation for recoverable/nonrecoverable paraplegia. We could also establish the guidelines for surgical decompression, indication of instrumentation, prediction of final kyphosis, and correction of kyphotic deformity. Optimum duration of anti-tubercular chemotherapy is still under study. Still we have not been able to define the end point of disease so that an optimum duration of ATT could be established. Maybe in future PET may help us in resolving this issue. We are very much aware that demonstration of drug resistance in osteoarticular lesions may not be possible due to its being paucibacillary disease, hence we may have to define clinical criteria to label suspected drug resistance particularly when cytological/histological evidence of active disease is present after a significant duration of ATT intake. Currently, we are working on: (a) Evaluation of PET to define the end point of treatment and (b) drug resistance in spinal TB.

Working for 25 years over 3000 patients, 38 publication, 22 research question could contribute significantly in solving unresolved gaps in the knowledge on spinal TB.²⁸⁻³⁵ Recently, participated in framing guidelines for treatment

of bone and joint TB as a team lead in collaboration with the ministry of health and family welfare and Cochrane collaboration. We could give recommendations on most of the issues with a very low evidence available and lot more work is still to be done. We are able to define the presumptive case, algorithm for diagnosis, drug treatment protocol, followup protocol, role of surgical intervention with indications of surgery, case definition of suspected drug resistance, use of gene expert, and other similar questions.

GROWTH OF SCIENCE

The water molecule in the body due to their thermal energy exhibit a random translational moment, termed Brownian motion or diffusion. Thus, produces lots of movement occurring in multiple heterogeneous directions, neutralizing each other molecule but the distance traveled is almost nil. However in biological tissues (axons), the mobility is restricted in all directions except in a particular direction. The diffusion is termed as anisotropic, and distance traveled by nerve impulse is one of the fastest.

Similarly, in science if the thought process is allowed to work in multiple directions than effective output is very low even if a clinician is working overtime to solve multiple heterogeneous research questions. Although one is able to publish lots of research papers, but it does not bring a perceptible change in clinical practice. One small research question may answer a small query. To change a practice one requires a series of research questions to be answered.

The ant moves in one direction taking a small piece of food, and it ends up in collecting a large volume of food collection in the hideout. Similarly, if a clinician works slow and steady by a series of research questions and by sustained focused efforts, the research output can change the clinical practice. It is well said by Mark Twain that "The secret of getting task ahead is getting started." The secret of getting started is breaking your complex overwhelming tasks into a smaller manageable task than starting on the first one. Success is the sum of small efforts repeated day in and day out.

Acknowledgment

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