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Original article

Acute coagulofibrinolytic and inflammatory changes in response to intramedullary nailing and its impact on outcome☆

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1. Introduction

Intramedullary nailing is the preferred course of care for the definitive management of femoral shaft fractures. Despite the superior biomechanical advantages over other implants, its use has been debated due to its possible harmful systemic effects in the patient experiencing trauma. Systemic inflammatory response, also called "first hit," after injury is followed by counter inflammatory response, which is a hypo-inflammatory reaction to counter severe inflammation. Any further thrust, by an extensive invasive surgical, can lead to "second hit," ending with acute respiratory distress syndrome (ARDS) multiple organ failure (MOF) and death.[1] Inflammatory reactions in response to injury are exacerbated by femoral nailing resulting in a hyper inflammatory reaction which is followed by hypo inflammatory phase.[2]

2–3% of isolated fracture shaft of femur patients develop, respiratory failure (RF) secondary to fat embolism, ARDS, pulmonary embolism. Rate of respiratory failure increases and ranges from 10 to 75%, in fracture shaft of femur with associated injuries depending on the method of surgical management.[3]

Intravasation of bone marrow and intramedullary fat[4], causes systemic intravascular coagulation and fibrinolysis with aggregation of platelets and formation of fibrin clots[5–6]. Inflammation potentiates coagulation with increased risk of thrombosis and down regulation of protein C anti-coagulant pathway.[7]

Excessive and uncontrolled activation of the coagulative, fibrinolytic and inflammatory pathways and hemodynamic changes have been implicated in some patients with isolated femoral shaft fractures, potentially worsened in those with concomitant injury. However, the pathophysiology of this condition remains incompletely understood.

The aim of this study was to examine the coagulative and inflammatory response following intramedullary nailing (IMN) procedure in fracture shaft of femur. Our hypothesis with the primary objective of evaluating the trends in the levels of thrombin/antithrombin, routine coagulation assays and Interleukin 6 (IL-6) following IMN & secondary objective was to compare the post-operative changes in these markers between the following study (I, II) and control (III) groups:- Study group: isolated fracture shaft of femur & polytrauma with fracture shaft of femur undergoing IMN and Control group: Patients undergoing plating of distal fracture femur.

2. Methods & methodology

2.1. Study design

Prospective observational cross sectional study

2.2. Level of evidence

Level II

☆ This study was presented at TRAUMA 2014, 27th–30th Nov 2014 in New Delhi, India. This study was presented (poster) at 38th *SICOT* Orthopaedic World Congress 2017, 30th Nov to 2nd Dec 2017 in Cape Town, South Africa.

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2.3. Setting

This study was conducted in the Department of Laboratory Medicine and Orthopedics, of a Level I Trauma Care Center in northern India, over a period of two years (2012–2014). Patient recruitment was done in the emergency room by orthopedic surgeons, and followed up to one year in the outpatient department, following informed consent. Approval from the Institute Ethics Committee was obtained prior to conducting this study [IEC/OP-1/2013].

2.4. Participants

Sixty orthopedic trauma patients undergoing intramedullary nailing procedure admitted during study period, were included in the study and categorized as Group I (Isolated fracture shaft femur) and Group II (Polytrauma (Any other injury other than Isolated fracture femur and/or Injury to any other organ system) along with isolated fracture shaft femur) based on the type and severity of injury. Fifteen patients undergoing external fixation of distal fracture of femur formed Group III (control). Patients with prior H/O (1) open grade II and II femoral shaft fractures, pathological fractures other than osteoporosis, (2) severe hypoxia, hypotension, acidosis and/or traumatic brain injury at the time of admission, (3) presence of metabolic bone disease, liver and renal insufficiency, (4) presence of inflammatory pathologies, systemic disorders (SLE), solid or hematological malignancies, (5) previous operation on the injured limb, (6) also patient taking long term nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelets, anticoagulants, steroids, immunosuppressive agents, antiresorptive agents, and parathyroid hormone were excluded along with secondary admissions. Also patients with incomplete follow up were retrospectively excluded.

Demographic data included age, sex, severity of injury, mode of injury, hospital length of stay, along with surgery related details such as: duration of surgery, time elapsed from injury to surgery, and whether the fracture site was opened during surgery or not, along with the clinical and laboratory investigations throughout hospital stay were recorded.

2.5. Surgical technique

Patients presenting at the emergency department were optimized according to the Advanced Trauma Life Support (ATLS) protocol, and were put on skeletal traction, if delay was anticipated, till the time of operation.

Isolated shaft femur fracture patients were operated at the earliest opportunity once they were optimized. Polytrauma patients were stabilized first with an external fixator within 48 h from injury and then operated for definitive fixation with reamed interlocking nail when deemed stable to undergo the procedure.

All the study patients were operated with standard closed antegrade IM nailing on fracture table under spinal or epidural anesthesia. Nails were locked both proximally and distally in all patients. Every attempt was made to perform the procedure closed however, in cases with delay if the reduction was not achieved mini open reduction of the two fragments was performed. Patients with distal femur fractures which were managed with external fixator initially and then definitively by plate were taken up as a control group. Plate application was also done once the patient was stabilized. Till then external fixator provided the splintage required.

2.6. Investigations

6 ml of blood samples were withdrawn preoperatively, post-operative at day 3, and 5 for all cases in group I and group II patients. For the group III (control) 6 ml of blood samples were withdrawn preoperatively and post-operative at day 3. Plasma based coagulation assay (prothrombin time, activated partial thromboplastin time, international normalized ratio, D-dimer & fibrinogen) along with ELISA analysis of Thrombin/Anti-thrombin complex (IMUBIND® TAT ELISA; catalog #ADG833, Sekisui Diagnostics GmbH) & Interleukin-6 (Human IL-6 Platinum ELISA, catalog #BMS213/2, eBiosciences, Vienna, Austria) were conducted as per manufacturer's instructions and data was maintained on a pre-designed pro-forma.

Any potential biased was addressed as the recruitment and laboratory investigations were performed by different individuals.

2.7. Outcome measure

The patients were mobilized from postoperative day one. Post-operative complications such as fat embolism syndrome, deep vein thrombosis, coagulopathy (defined as above than normal range of PT (16-2-16s), aPTT (28–36 s) and INR (<1.0)), sepsis (positive peripheral blood culture) and Acute respiratory distress syndrome (ARDS)[8] were assessed throughout the course of hospital stay. After discharge, patients were scheduled for regular clinical, radiological and hematological follow-up in outpatient department at predefined time interval. Each patient underwent standard rehabilitation protocol; initial toe-touch weight bearing mobilization was commenced as tolerated from immediate post-operative period, which gradually progressed to partial weight bearing after 4 to 6 weeks. Full weight bearing mobilization was instituted after clinical and radiological confirmation of bony union, which was defined as union of 3/4 cortices on two orthogonal radiographs and absence of pain with weight bearing with/without support.

2.8. Statistical methods

Data was summarized as Mean ± S.D, differences within the groups were compared by *T*-Test/Mann Whitney test. Analysis of variance (ANOVA), followed by repeated measure analysis was applied to compare between study group (I & II) & control group (III) and between pre and post-surgery samples. P value of <0.05 was considered to be statistically significant. GEE population-averaged model was applied followed by repeated measure analysis to estimate the parameters of a generalized linear model with a possible unknown correlation between outcomes were done.

3. Results

3.1. Participants

A total of 86 orthopedic trauma patients were recruited in the study, however 10 were excluded due to incomplete follow-up. One polytrauma patient who developed acute pancreatitis following pancreatic and common bile duct injury with femoral fracture, died in the second week of the postoperative period cause of death being septic shock, was retrospectively excluded. 75 Patients were included, 58 men in the study group and 14 men in the control group, aged 27.1 ± 11.08 and 27.6 ± 11.5 years, respectively. ISS was 11.6 ± 3.85 for the study group and 10.7 ± 5.1 for control. The time from injury to admission was 2(1–19) days for the study group and 4.5 (1–30) days for control. The fractures were classified according to AO/OTA Classification. Study control had

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