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Current Concepts in Orthopedic Management of Multiple Trauma

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Abstract: Multiple trauma patients frequently present challenging clinical scenarios with musculoskeletal injuries being the most common indications for surgical procedures in these patients. Despite our substantial knowledge, a universally approved objective definition for "multiple trauma" is yet to be delineated. Several controversial aspects of economics, pathophysiology, animal models, diagnosis, management and outcome of patients with multiple trauma have recently been explored and although some progress has been made, it seems that the available evidence is still inconclusive in some occasions. This manuscript revisits several current concepts of multiple trauma that have been the focus of recent investigation. We aim to provide the reader with an updated perspective based on the most recently published literature in the field of multiple trauma.

Keywords: Damage control, early total care, fracture, multiple trauma, orthopedics, sepsis, systemic inflammatory response syndrome.

INTRODUCTION

In patients with multiple trauma, musculoskeletal injuries are the most common lesions requiring surgical intervention with survivors frequently presenting challenging scenarios in terms of functional outcome and quality of life [1, 2]. The presence of extremity injuries in polytrauma patients have been reported to be associated with worse outcome, longer hospital stay and more need for blood transfusions [2]. Despite establishment of safety rules and advances in prevention and mitigation of severe injuries such as safety features of motor vehicles and more meticulous attention to safety details in professional and athletic conditions, these injuries continue to occur [3]. Multidisciplinary teamwork, appropriate resuscitation, judicious and appropriate use of adjunctive diagnostic methods and well-planned management strategies under consideration of time sensitivity are major elements of success in addressing life-threatening and debilitating consequences of multiple trauma.

Most of the available clinical evidence in multiple trauma is based on single-institutional retrospective studies with small sample size. There seems to be essential need for prospective well-designed clinical studies in this field and multi-institutional studies may be a solution to overcome the problem of sample size for less common clinical scenarios. In this manuscript, we present a synopsis of the most relevant topics related to orthopaedic trauma investigated in the past two years.

SEARCH STRATEGY AND SELECTION CRITERIA

The English language literature available in MEDLINE was searched from January 2012 to August 2014 using the query of "multiple trauma" in the MeSH (Medical Subject Headings) database with all its subheadings. 744 potentially relevant publications were found and reviewed in abstracts. This manuscript represents our interpretation and conclusion of 66 original papers that were deemed as relevant to our topic of interest and reviewed in full text.

DEFINITION

The term "multiple trauma" is used interchangeably with "polytrauma", "major injury" and "severe trauma" [4]. It defines trauma patients whose injuries involve multiple body regions, organ systems or cavities. However, considerable inconsistency exists for the definition of "multiple trauma" in terms of number of injuries, body regions or organs involved, pattern or mechanism of injuries and severity of injury. Butcher and Balogh, stated that based on the Abbreviated Injury Scale (AIS), two points or above in at least two body regions embrace the greatest percentage of the worst outcomes and significantly larger percentage of the multiple trauma patients [4, 5].

The trauma surgeons still lack consensus and should agree on a universal, comprehensive and validated definition for multiple trauma. The subjective definition of multiple trauma can differ across and even within the institutions [4]. Lack of an agreed definition affects classification of patients and consequently leads to difference in treatment strategies. With our increasing understanding of the inflammatory response to trauma, physiological derangement has recently been added as a new dimension for the definition of multiple trauma though an appropriate parameter for this element has not been defined, yet [6]. The ideal definition of multiple trauma should be reproducible, sensitive and specific, readily available at the early phase of resuscitation and capable of capturing both physiological and anatomical elements of multiple trauma [7] and helpful in planning treatment strategies. Such a consensus would substitute intuitive

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definitions, establish the basis for future research and would make it possible to compare datasets and conduct multi-centric studies.

EPIDEMIOLOGY

Understanding of the mechanism of injury, physiological responses to trauma and appropriate clinical approach to patients are important. However, the trauma community should also consider the significant impact of traumatic injuries on the society. Trauma caused by natural and man-made accidents is still considered as a major cause of mortality and morbidity on global scale [8]. Based on Nationwide Inpatient Sample (NIS) data, the incidence of unstable pelvic fractures has not changed and its associated in-hospital mortality has remained around 8% in the United States between 2000-2009 [9]. However, data from German Registry in the period of 2002-2011 showed a decrease in overall mortality. The same study found that mortality in association with multi-organ failure decreased in the same period despite increasing incidence of multi-organ failure in multiple trauma patients [10]. According to the Institute of Health Metrics and Evaluation, injuries accounted for 11% of global mortality and 13% of all disability-adjusted life-years [8].

ECONOMIC ASPECTS

Polytrauma requires a costly management including emergency care, imaging and other diagnostic studies, surgical operations, extended postoperative hospital stay with sometimes intensive care unit (ICU) stay, and prolonged rehabilitation programs [11]. The costs are expected to increase logarithmically by 2030 and the road injuries are expected to cost 518 billion US Dollars globally. Nevertheless, 90% of this burden is expected to occur in low- and middle-income countries [8]. There is considerable variation in the reported costs according to the country, trauma subgroups, the predictors of cost and the method of calculation [11]. Some economic evaluations have focused on the direct costs of medical treatment while others have also included the indirect costs of trauma, such as the opportunity cost of labor forgone [12]. New studies are needed to estimate the all costs for multiple trauma management as well as optimize the treatments. Also guidelines should address the regional differences and needs to be flexible to be able to adjusted based on the infrastructure of local emergency department involved in trauma care of severely injured patients. Cost optimization in polytrauma patients requires education and orchestration of human resources. A systemic and team approach in the initial management of trauma patients improves cost efficiency.

PATHOPHYSIOLOGY

The inflammatory response is a major cause of morbidity and mortality following severe trauma. Intense systemic and local inflammatory reaction elicited by the injury can potentially be associated with multiple physiologic impairment including organ dysfunction and compromise of immune system by itself. Although many aspects of this induced immune disorder are yet to be understood, the activation of innate immune system seems to have a considerable role. One of the suggested mechanisms is activation of pro-inflammatory mediators such as mitogen activated protein (MAP) kinase c-Jun N-terminal kinase (JNK) and p38 MAP kinase in the cells of innate immune system which will lead to release of inflammatory cytokines. Activation of this system (at both levels of gene transcription and protein translation) was observed in the circulating monocytes of patients who died due to blunt multiple trauma and also in multiple trauma patients who received massive transfusion [13]. Similar studies are required to delineate molecular mechanisms and risk factors for other potential associations such as trauma induced coagulopathy [14, 15] increased susceptibility to infections [15] and fracture healing impairment [16].

Two studies from the same group studied the role of body mass index (BMI) in systemic inflammatory response and overall outcome in multiple trauma patients [17, 18]. Higher BMI (>30 kg/m^2) was associated with worse physiological scores of organ function, particularly lung function as well as increased mortality rate [17]. However, based on Systemic Inflammatory Response Syndrome (SIRS) scores, obese patients were not different from non-obese patients and in fact patients with high BMI had lower maximum SIRS scores and slower pace to reach their maximum SIRS scores [18]. These findings need to be validated in prospective comparative studies with better control over the confounding factors. Nevertheless, a recent experimental study showed obese rats subjected to severe orthopedic trauma were associated with more intense systemic inflammatory response and were more vulnerable to oxidative stress-induce pulmonary damage [19].

The two-hit theory in multiple trauma suggests the neutrophils and other effector arms of the immune system are primed by the initial injury and therefore become more vulnerable to subsequent inflammatory signals (such as surgeries, transfusions, infections and other complications). This phenomenon will increase the risk of post-surgical SIRS and subsequently multi-organ failure [20, 21]. However, the relationship of levels of inflammatory biomarkers and the second-hit has not been robust enough based on few small-size prospective studies available [20]. Similarly in a recent study, the immediate impact of intramedullary femoral nailing, as the second hit, on multiple trauma patients was not clearly observed in a non-comparative small size study measuring various indices of hemodynamic stability, coagulation, fibrinolysis, oxygenation and inflammatory cytokines in the blood using a pulmonary artery catheter before nailing [22]. Some indices (such as thrombin/anti-thrombin complex, tissue plasminogen activator and IL-10) were most elevated at the time of admission before surgery (first hit) and some others (such as tissue factor, plasminogen activator inhibitor, TNF-α, IL-6 and pulmonary shunting) showed late increase between 48-72 hours following surgery. However, other than a transient increase in pulmonary vascular resistance around 2 hours following surgery, none of the other indices were significantly affected by the surgery [22].

A recent field of research in trauma patients is the possible association between genetics and inflammatory response to trauma. Two studies from the same group have investigated the influence of short nuclear polymorphism within IL-6 [23] and IL-10 [24] genes with blood levels of these markers and lethal outcomes following severe trauma. They found no significant relationship for IL-6 and a potential trend for IL-10. The theory is in the preliminary stages and needs more investigation.

ANIMAL MODELS

Efforts for improving animal models of multiple trauma are still in progress [25-28]. Animal models (particularly large animal models) provide a good opportunity for studying pathophysiology of inflammatory response and multi-organ failure [29] as well as in-vivo assessment of novel treatment options in standardized and reproducible experimental conditions [26, 30]. These models can be based on isolated or combined injuries [25] and if properly designed can provide valuable and clinically relevant information [25, 26]. However, some models may have advantages over the others for a particular question. Potential shortcomings of the animal models are inter-species physiologic dissimilarities with humans such as differences in coagulation and immune system in porcine models. On the other hand the supine position of the animal models is not physiologic and can cause ventilation-perfusion mismatch and impaired oxygenation [25]. Moreover, most animal models of trauma are short-term models with focus on the first few hours after the insult. Therefore, they cannot simulate delayed reactions to trauma and are not helpful in investigating long-term complications of trauma (such as adult respiratory distress syndrome). Nevertheless, animal models can be useful for preliminary therapeutic interventions in multiple trauma patients. A recent experiment in pig model of multiple trauma suggested administration of ubiquitin during resuscitation period favorably modulates local inflammatory response to blunt trauma in the lungs so that it improves metabolic hemostasis, reduces accumulation of third space fluid and preserves arterial oxygenation [30]. In an experimental rat model study, use of allogenic bone marrow transplants following blunt multiple trauma was associated with improved healing of long bone fractures and the speed of physical function recovery yet it was associated with negative impact on recovery of red blood cell and leucocyte counts [31]. In another rat model study, use of an NADPH oxidase-inhibitor was associated with less severe lung injury in obese rats [19]. Finally, two swine model studies demonstrated resuscitation with fresh frozen plasma attenuated secondary brain injury [32] and platelet dysfunction [33] following severe trauma.

DIAGNOSIS

The assessment of multiple trauma patients consists of initial, second and tertiary surveys via precise and time-efficient physical examination. Clinical evaluation, if appropriately strategized, serves as a helpful screening tool in alert patients to avoid unnecessary adjunctive diagnostic tests even in the presence of distracting injuries such as head, torso and long bone injuries [34]. This evaluation should be timely and include the whole body since delayed diagnosis of functionally important injuries such as hand injuries are not uncommon particularly in the presence of high injury severity score (ISS) and low Glasgow Coma Scale (GCS) [35]. Other studies have described trauma team leaders without surgical training being as risk factor for missed injuries. This finding needs to be better investigated in a prospective manner and across multiple institutions. However, it may have considerable implications in management and education [36].

Ultrasound imaging particularly focused assessment with sonography for trauma (FAST) has been integrated into the care of multiple trauma patients. In patients with pelvic fracture, it seems that FAST serves mainly as a screening tool with high negative predictive value for detection of intra-peritoneal bleeding requiring intervention [37]. Positive findings in FAST do not necessarily indicate the necessity for an intervention to control the internal hemorrhage. Use of ultrasound imaging for diagnosis of long bone fractures in patients with multiple trauma is unreliable and not justified [38].

Severely injured patients are exposed to substantial doses of x-ray as part of their diagnostic and therapeutic interventions. Whole-body computed tomography (WBCT) scan has been recommended in patients with distracting injuries or decreased level of consciousness [39]. This technique can particularly be helpful in whom no significant hint is found during physical examination yet the mechanism of injury and the clinical scenario suggests potential presence of undetected serious injuries. The advantages are providing detailed information within short time, which can lead to rapid diagnosis and intervention [40]. Whether use of WBCT is associated with decreased short-term mortality is unclear based on the current available evidence. It is possible that such association exists for subgroups of multiple trauma patients such as those with head trauma or hypotension and WBCT findings may change management strategy in these patients. Nevertheless, the precise indications for WBCT are yet to be described and its indiscriminate use is unjustified considering radiation risk, time and cost [40]. As a matter of fact, a study found that the x-ray dose that trauma patients received during hospitalization was correlated with the injury severity score (ISS). Patients with ISS over 16 received a dose of 49 millisieverts (mSv) and all multiple trauma patients received a minimum dose of 20 mSv [41]. Of note, the recommendations of two different advisory organizations on the annual dose for workers who are exposed to work-related ionizing radiation is 20 and 50 mSv [41].

The phenomenon of "satisfaction of search effect" (i.e. one radiographic abnormality is missed in the presence of another) has been a matter of controversy. This phenomenon was recently revisited in a study on patients with subtle fractures in the context of distractive life threatening injuries needing immediate medical intervention [42]. The findings of this study performed on musculoskeletal radiologists challenged this conviction. However, as the authors agree, the study was conducted in a simulated context which is unable to reproduce many confounding factors in the real life such as availability of history and physical examination findings, high number of radiographic images to be assessed, experience of the reader, multiple distractive interruptions and the stress of time pressure or work overload.

Brachial plexus injury (BPI) is an uncommon yet serious injury in multiple trauma patients for which appropriate treatment requires timely diagnosis (usually within the first 3 months of injury). Because of its association with various upper and lower extremity fractures, multiple lesions (involving nearby and remote organs) and coma and absence of a specific concomitant pattern of injury, BPI can be easily missed [43]. Therefore, this injury requires high index of suspicion particularly in multiple trauma patients with upper limb weakness and fractures of the shoulder girdle [43].

Use of biomarkers capable of predicting potentially preventable adverse outcomes in patients with multiple trauma continues to be an interesting topic of research. A recent study has suggested S100B measured during the first 24 hours after injury predicts hemorrhagic shock and its associated multiple organ failure and mortality [44]. Clara cell protein-16 has been introduced as a biomarker in serum and alveolar lavage fluid that is associated with loss of integrity of respiratory epithelium. Although this biomarker seems to be nonspecific to type of lung injury, Wutzler et al have suggested its initial elevation and second peak (later than 24 hours after the trauma event) in multiple trauma patients are associated with severe thoracic injury and late respiratory complications, respectively [45]. Septic complications are one of the major causes of late death in multiple trauma patients. An important element in successfully treating septic complications following multiple trauma is early distinction of sepsis from SIRS. A systemic review of biomarkers investigated for such a purpose did not find any single biomarker eligible for strong recommendation in clinical practice. Persistently elevated levels of procalcitonin may serve as an early indicator of posttraumatic sepsis and predict multi-organ failure and mortality [46]. Procalcitonin is a precursor of calcitonin hormone that is rapidly secreted from non-thyroidal cells in response to pro-inflammatory cytokines and bacterial products such as endotoxins. The use of biomarkers has been extended to other systemic complications of multiple trauma patients.

MANAGEMENT

The hemodynamic state of multiple trauma patients is a major determinant of optimal time for surgical stabilization of long bone and pelvis fractures. Although initial fluid resuscitation can normalize vital signs, persistently elevated serum lactate levels (> 2.5 mmol/L) can be sign of hypoperfusion and oxygen deficit at cellular level. This subclinical (or occult) hypoperfusion state was associated with increased need for inotropic agents during the first postoperative 24 hours, higher Sequential Organ Failure Assessment (SOFA) scores during the first week post surgery and longer duration of mechanical ventilation following fracture fixation. Elevated lactate levels may be representative of inadequate optimization of the patients for immediate fracture fixation procedures [47].

Data from German Registries showed severity of pelvic injuries correlates with the need for pre-hospital and intra-hospital fluid resuscitation [48]. The same study showed increased pelvic instability was associated with worse ICU outcomes (length of stay, days on mechanical ventilation, incidence of sepsis and multiple organ dysfunction syndrome).

Initial stabilization of the pelvic ring is of utmost importance in patients with multiple trauma and pelvis injury [49, 50]. However, some patients continue to remain hemodynamically unstable despite the resuscitation and on-site external pelvic ring fixation (such as a pelvic sheet or binder). The sequence of emergent interventions required in this critical condition is important. Therefore, algorithm-based approaches based on the hemodynamic status of the patients have been suggested although it is controversial whether hemodynamically stable patients with contrast extravasation on CT angiography benefit from embolization [49, 51]. Nevertheless, in the event of unstable patients with high ISS, bypassing the external fixation of pelvis and going directly for an intervention to stop a possible source of high-pressure bleeding (most commonly one of the branches of internal iliac artery) may be tempting. However, it has been shown that with nearly similar preoperative ISS, performing skeletal stabilization prior to other procedures such as intra-pelvic laparotomy with packing or angiography with embolization was associated with higher chance of survival [50]. Otherwise, the beneficial tamponade effect of external fixation will not be present at the time the tension-band mechanism of the abdominal wall is eliminated during laparotomy. Moreover, the source of blood is posterior venous plexus of the pelvis or the opposing surfaces of the fractured cancellous bone in most of the patients, and even in the case of a bleeding arterial branch, the source of bleeding is not always found rapidly during angiography. Therefore, doing such procedure without prior stabilization of pelvis assumes an unreasonably high risk [52]. Both laparotomy with packing and angiography with embolization can be successful in controlling retroperitoneal bleeding, although the latter requires a well-equipped facility with interventional radiologist.

EARLY APPROPRIATE CARE *VERSUS* DAMAGE CONTROL STRATEGY

Optimal timing of definitive fracture stabilization in multiple trauma patients has probably been one of the most controversial topics in recent years. Risk-adapted approaches based on anatomic location and severity of injury have been suggested for making decision whether to perform primary definitive treatment within the first 24 hours after trauma (Early Total Care, ETC) or rapid provisional stabilization of the fracture in the immediate state (external fixation or traction) and postponing the definitive surgery to a more stable condition some days later (i.e., Damage Control Orthopedics, DCO). However, there is no universally agreed criteria for indicating ETC or DCO [53, 54]. A retrospective comparative study on patients with multiple trauma admitted to two level-I trauma centers in Germany and Australia shows the difference in attitude between surgeons. Having patients with similar ISS, the use of ETC *versus* DCO was 70 *versus* 30% in Australia and 30 *versus* 70% in Germany, respectively. The median ISS for ETC patients was 34 and 25.5 for Australian and German hospitals, respectively. Interestingly, surgeons in the German hospital had lower threshold for indicating DCO for patients with traumatic brain injury compared with their Australian counterparts [54]. Advocates of ETC insist in advantages of early fixation such as lower rates of pulmonary complications, shorter hospital and ICU stays, fewer ventilator days and lower hospital charges [55]. The challenge is to distinguish whether these advantages are because of ETC by itself or due to lower injury severity in patients undergoing ETC compared with those undergoing DCO. However, some authors suggest that in cases of uncertainty, DCO is a safer strategy [53, 56]. Data from Registry of German Trauma Society regarding multiple trauma patients with bilateral femoral fracture shows recent trend toward DCO philosophy in this condition [56]. However, when adjusted for ISS, DCO and ETC had similar mortality rates, confirming that ETC strategy, if appropriately indicated, does not increase mortality. The study concluded that increased ISS, presence of severe thoracic injury and coagulopathy are the risk factors with highest early mortality and organ failure following ETC in multiple trauma with bilateral femoral fracture [56].

Another controversial aspect of management of multiple trauma patients is optimal time for fixation of associated vertebral fractures, with ETC [defined as surgical fixation within the first 72 hours after the traumatic event] being considered advantageous in terms of earlier ambulation, lower risk of secondary neurologic complications, shorter hospital and ICU stay, lower incidence of surgical pulmonary complications and fewer general complications (deep vein thrombosis, urinary infections, wound related issues, pressure ulcers) and less overall cost [57, 58]. Spine damage control (SDC) approach has been proposed as the modification of DCO for unstable thoracic and lumbar vertebral fractures that require anterior stabilization or anterior spinal cord decompression. This is a staged procedure during which immediate reduction and posterior instrumentation is performed within the first 24 hours after trauma and the second stage (360° completion fusion) is performed within 72 hours [59]. A prospective randomized study to assess the benefits of this concept is missing but a few recently published retrospective studies evaluated this issue with two different approaches [58-60]. Based on a single institutional US study including 112 consecutive patients, the patients who underwent SDC protocol (mean time to the first and second surgery were 9 and 207 hours, respectively), compared with those undergoing delayed surgery (on average 99 hours following trauma), had shorter operative time (2.4 *versus* 3.9 hours, respectively), shorter hospital stay (14 *versus* 33 days, respectively), shorter ventilation-dependency time (2 *versus* 9 hours, respectively) and lower incidence of early postoperative complications (wound complication, urinary tract infection, pressure ulcer and pulmonary complications) [59]. These findings were in agreement with those reported by a German Trauma registry based study consisting of 4354 patients with severe spinal injuries (AIS≥3) between 1993 and 2010 comparing early (<72 hour) *versus* delayed vertebral fixation [58].

An important aspect of surgical management of multiple trauma patients is high potentiality for infectious complications (including surgery-related and non-surgery related infections) either due to immunosuppression induced by the stress of initial trauma, the nature of injuries or iatrogenic causes. Concerns may exist regarding the risk of hematogenous spread of remote infections to the site of orthopedic procedure. However, data regarding 179 femoral or tibial internal fixation procedures in 128 patients admitted to trauma ICU who showed fever before surgery or presence of remote infection in the perioperative period was associated with 5.6% rate of acute postoperative infection [61]. Although control group was missing in this study, the risk of infection does not seem to be too high to preclude an internal fixation surgery that favorably affects the final outcome of these patients.

OUTCOME/PROGNOSIS

Comparison of outcome and mortality in multiple trauma patients is challenging because of the complexity and multifactorial nature of the insulting trauma by itself and also due to difference in the existing definition systems. Although various parameters have been described to predict outcomes in these patients, the value of predictive factors depends on the characteristics of patient population. However, identification of predictive factors allows for optimization of modifiable risk factors and appropriate adjustment of treatment plan to address non-modifiable risk factors.

A recent prospective study performed on patients with multiple trauma and moderate ISS scores who had been cleared for major surgery found decreased GCS levels and presence of lung contusion were associated with higher risk of postoperative complications [62]. Another retrospective study described tachycardia and hyperglycemia as well as multiple preexistent comorbidities and thoracic spine trauma as predictive of suboptimal physical health status within the first 48 hours after admission [63].

Based on data available from German Trauma Registry between 2004-2011, major risk factors for in-hospital mortality after pelvic fracture were mainly indices of hemorrhage such as presence of massive bleeding particularly from pelvic region (the most common associated factor with mortality), lower initial blood hemoglobin concentration, lower systolic arterial blood pressure and the number of transfusion units. Critical thresholds for these variables were not describe. Other risk factors were male gender, complex pelvic injuries [defined as type B and C of Tile classification associated with major visceral, neurovascular or soft tissue injuries] and higher ISS scores [64]. In a totally different clinical setting, other investigators reported similar risk factors for mortality in patients with combat-related pelvic fracture, with Tile classification being predictive of mortality when controlling for large vessel and brain injury [65]. Additionally, a single-institutional retrospective study found that although the mortality associated with unilateral and bilateral femoral fractures decreased compared with a historical control group 15 years earlier (12 *versus* 2% for unilateral and 26 *versus* 7% for bilateral femoral fractures), bilateral femoral fractures were still significantly associated with mortality compared with unilateral femoral fractures [66]. Although this association has partially been attributed to the severity of associated injuries in bilateral femoral fractures, the findings of a recently published study by Kobbe *et al.* challenge the role of bilateral femoral fracture as an independent risk factor for mortality [67]. In their retrospective study based on German Trauma Registry between 2002-2005, 776 patients with unilateral and 118 patients with bilateral femoral fractures were recruited. Higher ISS scores, increased incidence of pulmonary and multi-organ failure, more severe abdominal injuries, massive transfusion and higher mortality rate were observed in the bilateral group, yet only pulmonary failure had independent association with bilateral femoral fracture in the multivariate analysis. Interestingly, subgroup analysis showed in patients with equal ISS scores the influence of an additional femoral fracture on pulmonary and multiple organ failure was more prominent in lower ISS scores and with the increasing severity of injury (higher ISS scores), an extra femoral fracture did not have such systemic impact.

Patients subjected to trauma are at increased risk of hypercoagulability state. Potential risk factors are location and severity of injury, hemorrhage, iatrogenic interventions (surgeries, transfusions, central venous catheters), longer hospital stay and immobilization. Using thromboelasto-graphy or TEG (a diagnostic assessment of the parameters of physiologic process of coagulation), it was observed that 85% of trauma patients with Greenfield 's risk assessment profile (RAP) score above 10 at the time of trauma ICU admission were at hypercoagulable state that would not be detected by routine coagulation tests [68]. The risk existed in the majority of patients despite administration of thromboprophylaxis protocols for one week. Administration of tranexamic acid did not increase risk of venous thromboembolism (VTE) in these patients yet increased age, longer ICU stay and no thromboprophylaxis did increase the risk of VTE. However, neither TEG nor coagulation tests were able to predict occurrence of VTE.

FUTURE DIRECTIONS

Despite considerable innovations and advances of our understanding of various aspects of multiple trauma patients, many issues remain controversial. Lack of high-level evidence with adequate size seems to be the major limitation for clinical studies.

One of the most essential issues to resolve is to reach into an agreement for the definition of multiple trauma. Many aspects of the molecular and cellular mechanisms of the local and systemic immune response to severe trauma such as pathophysiology of organ dysfunction and bone healing need to be better elucidated. Moreover, translational studies to incorporate our molecular knowledge into efficient clinical strategies are lacking. There is no reliable parameter to determine optimal time of surgical intervention or to distinguish patients at risk of organ failure. Individualization of the management plan has been suggested [1]. This strategy considers individualized goals for initial resuscitation and also adaptation of surgical strategy (early total care, minimally invasive early total care or damage control) based on the clinical scenario. Most importantly, optimal timing for initial and definitive fixation of the fractures requires definition of appropriate outcome parameters. These parameters should be well correlated with general physiologic state of the patient as well as characteristics of the local injuries.

ABBREVIATIONS

AIS	=	Abbreviated Injury Scale
BMI	=	Body Mass Index
BPI	=	Brachial plexus injury
DCO	=	Damage Control Orthopedics
ETC	=	Early Total Care
FAST	=	Focused Assessment with Sonography for Trauma
GCS	=	Glasgow Coma Scale
ICU	=	Intensive Care Unit
ISS	=	Injury Severity Score
JNK	=	c-Jun N-Terminal Kinase
MAP	=	Mitogen Activated Protein
MeSH	=	Medical Subject Headings
mSv	=	MilliSieverts
NIS	=	Nationwide Inpatient Sample
SDC	=	Spine Damage Control
SIRS	=	Systemic Inflammatory Response Syndrome
SOFA	=	Sequential Organ Failure Assessment
VTE	=	venous thromboembolism
WBCT	=	Whole-Body Computed Tomography

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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