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Dr. Naeem Jagani
 DNB Ortho. Consultant,
 Department of Orthopaedics, Guru
 Nanak Hospital, Mumbai,
 Maharashtra, India

Dr. Lokesh Sharoff
 DNB Ortho. Fellow, Department
 of Orthopaedics, P.D. Hinduja
 Hospital, Mumbai, Maharashtra,
 India

Dr. Sudeep Nambiar
 DNB Ortho. Department of
 Orthopaedics, P.E.S Institute of
 Medical Science and Research,
 Kuppam, Chittor, Rajasthan,
 India

Dr. Jonathan J D'souza
 DNB Ortho. Senior Registrar,
 Hamdard Institute of medical
 sciences and Research, HAHC
 hospital, New Delhi, India

Dr. Chirag Borana
 DNB Ortho. Consultant,
 Department of Orthopaedics,
 Masina Hospital, Mumbai,
 Maharashtra, India

Dr. Nadir Shah
 MS Ortho. Assistant professor,
 Department of Orthopaedics, Sir
 JJ group of hospitals, Mumbai,
 Maharashtra, India

Correspondence

Dr. Lokesh Sharoff
 DNB Ortho. Fellow, Department
 of Orthopaedics, P.D. Hinduja
 Hospital, Mumbai, Maharashtra,
 India

Functional outcome of primary flap coverage and bony fixation of severe open fractures: A prospective observational study

Dr. Naeem Jagani, Dr. Lokesh Sharoff, Dr. Sudeep Nambiar, Dr. Jonathan J D'souza, Dr. Chirag Borana and Dr. Nadir Shah

Abstract

Introduction: Improved understanding of open fracture pathology, techniques of fracture fixation, soft-tissue care, and antimicrobial treatment has resulted in a significant reduction of morbidity and mortality associated with open fractures. Yet, the most severe open fracture types, even in the hands of experienced trauma surgeons, are still fraught with complications and impaired function. Major advances over the last century have moved the focus of management of such injuries beyond the preservation of life and limb to preservation of function and prevention of complications. In this series, we present a two year experience in the management of severe open fractures, Gustilo types IIIA and IIIB, with the use of free muscle flaps and overlying skin graft for their soft tissue reconstruction.

Aim: The study was conducted to assess the functional outcome of severe open fractures treated by primary soft tissue/flap coverage and bony fixation.

Materials and Methods: 35 patients with single segment (i.e thigh, leg, arm, forearm) injury were selected for the study and treated in a tertiary care hospital. Patients were evaluated clinically and radio graphically and those with type 3A and 3B Gustilo-Andersons injuries were selected and treated by thorough and radical debridement, bony fixation and soft-tissue coverage within 72 hours. Patients were followed up for a minimum period of 12 months. The post-operative complications, time taken for bony union, stability of scar, the range of movements of proximal and distal joints and the SMFA (Short Musculoskeletal Functional Assessment Questionnaire) were taken for the assessment of functional outcome.

Results and Discussion: Results of SMFA were good in 20, fair in 9 and poor in 6 patients.

Conclusion: This Fix and Flap protocol leads to a drastic reduction in infection rates and primary flap coverage has several other advantages both to patients and care givers in the form of reduction in length of hospital stay, cost of treatment, time spent in rehabilitation and most importantly the number of surgeries or debridements a patient must undergo. This method thus leads to a drastic reduction in physical, psychological, financial and social repercussions on the individual.

Keywords: primary flap coverage and bony fixation of severe open fractures

Introduction

Open fractures mean communication between the external environment and the fracture and have been described as a soft-tissue injury complicated by a broken bone. Four components characterize the injury: Fracture, soft-tissue damage, neurovascular compromise, contamination.

The extent of each component must be assessed individually in order to achieve a comprehensive understanding of the injury, upon which a treatment plan can be based. Improved understanding of open fracture pathology, techniques of fracture fixation, soft-tissue care, and antimicrobial treatment has resulted in a significant reduction of morbidity and mortality associated with open fractures. Yet, the most severe open fracture types, even in the hands of experienced trauma surgeons, are still fraught with complications and impaired function.

Severe open injuries, regardless of the location and extent, are today managed by early aggressive debridement and early definitive reconstruction can be initiated once the deliberation over whether to salvage or amputate has been resolved. This requires experience and special skills, cooperation of plastic, vascular, and orthopedic surgeons, support staff and services, and specialized equipment in modern trauma centres ^[1, 2]. Major advances over the last century have moved the focus of management of such injuries beyond the preservation of

life and limb to preservation of function and prevention of complications.

In this series, we present a two year experience in the management of severe open fractures, Gustilo types IIIA and IIIB, with the use of free muscle flaps and overlying skin graft for their soft tissue reconstruction. Apart from a drastic reduction in infections, primary flap coverage has several other advantages both to patients and care givers in the form of reduction in length of hospital stay, cost of treatment, time spent in rehabilitation and most importantly the number of surgeries or debridements a patient must undergo.

Aim

The study was conducted to assess the functional outcome of severe open fractures treated by primary soft tissue/flap coverage and bony fixation.

Materials and methods

A sample size of 35 patients (29 males and 6 females) were selected in a tertiary care teaching institute(Chennai)for a period of 2 years from September 2012- September 2014 with a minimum follow up of 1 year duration.

All patients presenting to the hospital with grade 3A &3B open fractures during the aforementioned period of time were included in the study.

Inclusion criteria included- 1. Age between 15-60 years, 2.Wound coverage by 72 hours after injury (primary), 3.Isolated single segment (thigh, leg, arm, forearm) injuries only and 4. Gustilo-Anderson type 3A &3B compound fractures (SEVERE), 5. Written and informed consent obtained from the patient.

Exclusion criteria included – 1. Diseases such as Diabetes Mellitus, Rheumatoid Arthritis, coagulopathies, cirrhosis, severe anemia.2. Multiple injuries – Head injury, abdominal injury, chest injury and other limb injuries were also excluded. 3. Immunosuppression- pharmacological or disease induced. 4. Substance abuse (nicotine, alcohol, illicit drugs). 5. Unstable socio-economic status (housing, nutrition, caretakers). 6. Neuropsychological ailments (treated or otherwise).

The patients were seen in the emergency department and resuscitation was done if needed and detailed history and examination was carried out. The wound was classified according to the Gustilo-Andersons classification before debridement and radiographs were taken of the affected site including the proximal and the distal joints. Wound swab was taken and sent for pus culture and sensitivity. Wound wash with 4 liters of normal saline was given and betadine soaked dressing was applied.

Antibiotics – Injection: Cefuroxime 1.5 gm i.v and Gentamycin 80 mg i.v were given. In surgery, wound was washed with 5 L to 8 L of normal saline. Radical wound debridement was done and the wound was again classified by Gustilo-Andersons classification and the sites for flap and split skin grafts were marked. Bony fixation was done by external fixation / internal fixation by inter-locking nails/locking plates/dynamic compression plates. Temporary measures of wound coverage such as vac-u-seal dressing or epiguard dressing were used in certain cases to tide over the time lag between debridement + skeletal fixation and soft tissue coverage. Flap coverage was done. 6 cases had flap cover by medial gastrocnemius, 14 had antero-lateral thigh flap, 2 had ipsilateral bipedicle flaps, 3 had medial hemi-soleus flaps, 7 latissimus dorsi flaps and 3 gracilis flaps.1 unit of compatible blood was transfused during the surgery in most cases. Post-operative antibiotics were given according to the pus culture

and sensitivity report. Non weight bearing for 4 weeks and partial weight bearing for 4 to 6 weeks till the radiological union and later full weight bearing was allowed. Patients were followed up for a minimum period of 12 months in this period of study.

As the data thus collected was heterogenous (in terms of location of fracture; type of fracture; extent of bony comminution; the extent of soft tissue disruption; the type of skeletal fixation; the type of soft tissue reconstruction; total number of procedure; etc.) it was not possible to analyze the data with the standard statistical tests (viz. t-test; paired t- test; student t-test; chi-squared test; etc.) and was thence analyzed using percentages and averages; and patients were made to fill out the Short Musculoskeletal Function Assessment Questionnaire (SMFA).

A suitable conclusion was drawn based on the analysis.

Results

The post-operative complications, time taken for bony union, stability of scar, the range of movements of proximal and distal joints and the SMFA at 12 months were taken for the assessment of functional outcome and results [Table 1].

Table 1

	Age/Sex	MOI	GA-Type	Time lag (hrs)	MOFF	STC	BT	TCP	D	SP	NHA	SS	U(Wks)	Complications	C/R	FR
1	33/M	RTA	III-B	5	EX-FIX	ALT	1	E	2	EFR + N + FP + TFBG	3	Y	Y(17)		Good	CFR
2	19/F	FFH	III-A	6.5	LPLT	G + SSG	1	E	2	TFBG	2	Y	Y(12)		Good	CFR
3	27/M	RTA	III-B	8	N	ALT	2	E	3		2	Y	Y(20)		Good	CFR
4	29/M	RTA	III-A	11	DCP	ALT	0		2	BG	3	N	Y(18)	OM	Poor	N
5	49/M	RTA	III-A	6	N	ALT	2	E	1	AF + BG	2	Y	Y(12)		Good	CFR
6	35/M	RTA	III-B	4	N	ALT	1		2		1	N	Y(15)	SI	Good	CFR
7	24/F	RTA	III-B	4	EX-FIX	G + SSG	1	E	2	FP + TFBG	2	Y	Y(19)		Good	CFR
8	42/M	RTA	III-A	7.5	N	ALT	2	E	2	FP + TFBG	2	N	Y(20)	C/A	Fair	N
9	20/M	RTA	III-B	9	N + DCP	G + SSG	1	V	3	AF + BG	2	Y	Y(17)		Good	CFR
10	40/M	RTA	III-B	13	EX-FIX + N	G + SSG	3	V	3	BG	2	N	Y(19)		Good	CFR
11	33/M	RTA	III-B	16	N + MLW	ALT + SSG	0	V	1	FP + TFBG	2	Y	Y(22)	AKP + S	Fair	MFR
12	49/F	RTA	III-A	15	EX-FIX	BPF	0	E	1	EFR + N + FP + TFBG	2	Y	Y(26)	A	Fair	MFR
13	26/M	RTA	III-A	18	EX-FIX	MHS	2		1	EFR + N + FP + TFBG	3	Y	N	INU	Poor	N
14	43/F	RTA	III-A	3	N	ALT	2	E	1	FP + TFBG	2	Y	N	NU	Poor	N
15	31/M	RTA	III-B	4	N	MHS + SSG	1	V	2	BG	3	N	Y(24)		Good	CFR
16	34/M	RTA	III-B	9	N	Gracilis + SSG	3	V	2	FP + TFBG	3	Y	N	INU	Poor	N
17	44/M	RTA	III-B	9.5	N	ALT	4	E	2	FP + TFBG	2	Y	Y(18)	S	Fair	MFR
18	50/M	RTA	III-B	12.5	EX-FIX	LD	3	E	2	EFR + N + FP + TFBG	3	Y	Y(20)		Good	CFR
19	22/M	RTA	III-B	14	LPLT	LD	4	E	2	AF + BG	4	N	Y(26)		Good	CFR
20	29/F	RTA	III-A	7	LPLT	LD	0		2	AF + BG	3	Y	Y(28)		Good	CFR
21	30/M	RTA	III-A	8	LPLT	ALT	2	V	1	BG	2	Y	Y(30)	S	Fair	MFR
22	19/M	RTA	III-B	5.5	LPLT + DCP	ALT	1	V	1		2	Y	Y(26)		Good	CFR
23	38/M	RTA	III-B	6	N + DCP	LD	1	V	2		1	Y	Y(18)		Good	CFR
24	32/M	RTA	III-B	6	N + DCP	LD	3	V	2		2	Y	Y(16)	C/A	Fair	MFR
25	23/M	RTA	III-B	11	LPLT + DCP	ALT	2		2	BG	3	Y	Y(22)		Good	CFR
26	27/M	RTA	III-A	19	N	Gracilis+SSG	1		1	FP + TFBG	3	Y	Y(22)		Good	CFR
27	33/M	FFH	III-A	15	N	Gracilis+SSG	0	E	1	FP + TFBG	2	Y	Y(28)	AKP	Fair	MFR
28	41/M	RTA	III-B	18	N	G + SSG	1	E	3	FP + TFBG	2	Y	Y(22)		Good	CFR
29	33/F	FFH	III-A	11	N	G + SSG	0		1	BG	2	Y	Y(30)		Fair	CFR
30	38/M	RTA	III-B	5	EX-FIX	ALT	2	V	1	EFR + N + FP + TFBG	3	Y	Y(28)	DI	Poor	N
31	33/M	RTA	III-B	3.5	EX-FIX	ALT	2	V	2	EFR + N + FP + TFBG	3	N	Y(30)		Fair	N
32	48/M	RTA	III-B	8.5	EX-FIX	LD	2	V	2	EFR + N + FP + TFBG	2	Y	Y(22)		Good	CFR
33	50/M	RTA	III-A	7.5	N	BPF	1		1	FP + TFBG	2	N	N	INU	Poor	N
34	47/M	RTA	III-A	6	N + EX-FIX	MHS	2	E	1	FP + TFBG	2	Y	Y(26)		Good	CFR
35	46/M	RTA	III-B	11	LPLT	LD	3	V	3	AF + BG	2	Y	Y(24)		Good	CFR

SMFA

The results of SMFA were found as follows: Good --20 (57.14%), Fair – 9 (25.7%), Poor – 6 (17.4%).

Time lag between injury and surgery

The average time lag between injury and surgery was 9.22 hours.

Complications

Complications associated were anterior knee pain were observed in 2 cases, Superficial infection in 1 patient developed superficial infection, Deep infection developed in 1 of the cases, Non-union was observed in 4 cases, Cellulitis/abscess in 2, Osteomyelitis in 1, Joint stiffness in 3, Infected Non-union in 3, and Amputation in 1 case were observed.

Radiological Union

The Radiological union was sound at an average of 20.22 weeks among the 31 patients that achieved union and a stable scar was achieved in 27 cases.

Discussion

Millions suffer major limb injuries annually globally. As many of them sustain skeletal injuries, they reach orthopedic surgeons initially. Compound fractures, especially type IIB, are fixed well but sometimes, inexperienced orthopedic surgeons cannot address the soft tissue problems well. Especially over the lower leg where skin is not mobile and there is paucity of soft tissue, tension sutures are applied to pull and close the wound over the fracture site. These tricks do not usually work and the result is a wound with exposed bony fragments in its depth. These are often then subjected to multiple dressings only after which they are handed over to the trauma reconstructive surgeon for flap coverage. Wound coverage in this situation is fraught with complications of flap necrosis, wound infection and possibly sepsis and, chronic osteomyelitis. Quality of bony healing and consequently rehabilitation suffers. Unsatisfactory bone healing defers weight-bearing which has a significant negative impact in the lower limb salvage. Pioneering work by Godina proved superiority of early flap coverage when he reported 0.75% failure rate of free flaps done within the first 72 hours (primary) after trauma. The failure rate was 21.5% when the procedure was carried out later [3]. Cierny *et al* reported lower flap failure rate, deep infection rate and non-union rate of the fractures in the group with early wound coverage [4]. The problem of increased incidence of infection and ex-plantation after internal fixation in the patient with major limb trauma appears ill-founded in the face of current practice of aggressive debridement. Internal fixation, in the presence of a well-debrided and immediately covered wound, does not increase the rate of infection [5].

Thus there has been a paradigm shift from delayed soft tissue coverage for the compound fracture to urgent debridement and flap coverage. After initial adequate resuscitation and stabilization of the patient, the open fracture should be dealt with in the operating theatre as soon as possible, preferably within six hours of the injury [6]. Restoration of gross alignment of the limb should take priority in the initial management since obvious angulation and displacement or prominent bone fragments could exert undue pressure on soft tissues or neurovascular structures [7]. The distal arterial pulses, capillary refill and overall colour of the limb, and the presence of active bleeding from the wound must be recorded.

Although a thorough neurological examination is impossible at this stage, motor and sensory function should be noted. In severe trauma to the leg, preservation of plantar sensation has been thought to be an important prognostic factor in deciding whether salvage of the limb is worthwhile [8]. Specific environmental exposure should be carefully documented. Injuries in a farmyard or when heavily contaminated by soil are associated with *Clostridium perfringens*, and wounds exposed to the environment of a lake or a river carry the risk of infection by *Pseudomonas aeruginosa* or *Aeromonas hydrophilia* [9]. A digital photograph should be taken. Debridement and irrigation with sterile saline solution in the emergency room should be avoided in order to avoid inoculation of the deeper tissues with nosocomial micro-organism [10]. Nevertheless, irrigation of the open wound in the emergency room is advocated by some authors in the case of heavily contaminated wounds [11].

Early skeletal stabilization is of paramount importance and, ideally, should be performed at the time of the initial debridement. It restores alignment of the limb, eliminates gross movement at the site of the fracture, limits further soft-tissue damage and decreases the risk of further bacterial spread [12]. It also improves blood flow and venous return in the limb and reduces post-traumatic oedema, pain and stiffness [13].

The types of fixation currently available are external fixators, plates and screws, and reamed and unreamed locking nails. External fixators were considered to be the preferred method for obtaining bone stability [14, 15, 16, 17, 18]. The introduction of reamed locking nails was met with caution in case of an increase in complications, mainly in the form of infection and nonunion due to compromise of the cortical blood supply as a result of reaming [19, 20, 21]. The advent of unreamed locking nails sparked new interest in nailing open fractures [22]. The development of biological techniques in plate fixation and the design of implants which cause the least possible interference with the periosteal blood supply have enhanced the use of plates and screws for stabilization of even open tibial fractures. There are 3 randomized prospective trials comparing external fixation with modern unreamed intramedullary nailing [23, 24, 25]. There was no statistically significant difference between these two methods of stabilization with respect to union, delayed union, deep infection and chronic osteomyelitis. The use of external fixation was associated with a statistically significant increased rate of mal-union and further surgery whereas unreamed nailing showed a statistically significant increase in the rate of failure of the implant.

The increasing incidence of resistant nosocomial infections and the financial burden of a policy of delayed soft-tissue cover have prompted a re-evaluation of the care of open fractures [26]. The advent of early microsurgical free-flap transfer for complex trauma of the limbs has been a valuable advance [3], helped by the shift from external to internal fixation which has facilitated microsurgical soft-tissue reconstruction. A radical 'immediate' or 'very early fix and flap' protocol has developed, based on a close collaboration between orthopedic and microsurgical teams. A recent report on such management showed a rate of union of 100% although with delayed union in 62%, and of infection of 9.5% [27]. The main drawback is the need for a joint orthopedic and plastic surgery service, which is not feasible in many units, and the fact that major microsurgical procedures are contraindicated in patients with multiple injuries and hypovolaemic shock. Cole *et al.* [28] have proposed the use of local fasciocutaneous flaps for immediate cover of open fracture wounds.

Conclusion

The basic success of this study is very much dependent on the teamwork done by orthopedic surgeons, and plastic surgeons. By a single stage aggressive radical approach the patients who are bread winners of family are benefited and returned to normal activities in a faster period. The long hospital stay, expenditures to combat complications are avoided. By co-ordinated team work, continuity of care and a policy of early reconstruction and rehabilitation, the severe open fractures can be managed successfully. Thus it is evident that apart from a drastic reduction in infections, "primary flap coverage" has several other advantages both to patients and care givers in the form of reduction in length of hospital stay, cost of treatment, time spent in rehabilitation and most importantly the number of surgeries or debridements a patient must undergo. This method thus leads to a drastic reduction in physical, psychological, financial and social repercussions on the individual.

References

- Norris BL, Kellam JF. Soft-Tissue Injuries Associated With High-Energy Extremity Trauma: Principles of Management. *J Am Acad Orthop Surg.* 1997; 5(1):37-46.
- Templeman DC, Gulli B, Tsukayama DT, Gustilo RB. Update on the management of open fractures of the tibial shaft. *ClinOrthopRelat Res.* 1998; (350):18-25.
- Godina M. Early microsurgical reconstruction of complex trauma of the extremity. *Plast Reconstr Surg.* 1986; 78:285-920.
- Ciorny G, Byrd HS, Jones RE. Primary versus delayed soft tissue coverage for severe open tibial fractures. A comparison of results. *Clin Orthop.* 1983; 178:54-63.
- Rajasekaran S, Sabapathy SR. A philosophy of care of open injuries based on the Ganga hospital score. *InjuryInt J Care Injured.* 2007; 38:37.
- Gregory P, Sanders R. The management of severe fractures of the lower extremities. *Clin Orthop.* 1995; 318:95-105.
- Tscherne H. The management of open fractures. In: Tscherne H, Gotzen L, eds. *Fractures with soft tissue injuries.* Berlin: Springer-Verlag, 1984, 10-32.
- Lawrence RM, Hoepflich PD, Huston AC, Benson DR, Riggins RS. Quantitative microbiology of traumatic orthopaedic wounds. *J Clin Microbiol.* 1978; 8:673-5.
- Gustilo RB, Merkow RL, Templeman D. Current concepts review: the management of open fractures. *J Bone Joint Surg [Am].* 1990; 72:299-304.
- Advanced Trauma Life Support program for doctors. Sixth ed. Chicago: American College of Surgeons, 1997.
- Olson SA. Open fractures of the tibial shaft: current treatment. *J Bone Joint Surg [Am].* 1996; 78:1428-37.
- Worlock P, Slack R, Harvey L, Mawhiney R. The prevention of infection in open fractures: an experimental study of the effect of fracture stability. *Injury,* 1994; 25:50-72.
- Muller ME, Perren SM, Allgower M. *Manual of internal fixation: techniques recommended by the AO group.* 3rd ed. Berlin: Springer-Verlag, 1990.
- Behrens F, Comfort TH, Searls K, Denis F, Young T. Unilateral external fixation for severe open tibial fractures: preliminary report of a prospective study. *Clin Orthop.* 1983; 178:111-20.
- Behrens F, Searls K. External fixation of the tibia: basic concepts and prospective evaluation. *J Bone Joint Surg [Br].* 1986; 68:246-54.
- Burgess AR, Polca A, Brumback RN, Bosse MJ. Management of open grade III tibial fractures. *Orthop Clin North Am.* 1987; 18:85-93.
- Court-Brown CM, Wheelwright EF, Christie J, McQueen MM. External fixation for type III open tibial fractures. *J Bone Joint Surg [Br].* 1990; 78:801-4.
- Edwards CC, Simmons SC, Browner BD, Weigel MC. Severe open tibial fractures: results treating 202 injuries with external fixation. *ClinOrthop.* 1988; 230:98-115.
- Klein MPM, Rahn BA, Frigg R, Kessler S, Perren SM. Reaming versus non-reaming in medullary nailing: interference with cortical circulation in the canine tibia. *Arch Orthop Trauma Surg.* 1990; 109:314-16.
- Schemitsch EH, Kowalski MJ, Swiontkowski MF, Senft D. Cortical bone blood flow in reamed and unreamed locked intramedullary nailing: a fractured tibia model in sheep. *J Orthop Trauma.* 1994; 8:373-82.
- Court-Brown CM, McQueen MM, Quaba AA, Christie J. Locked intramedullary nailing of open tibial fractures. *J Bone Joint Surg [Br].* 1991; 73:959-64.
- Bone LB, Kassman S, Stegemann P, France J. Prospective study of union rate of open tibial fractures treated with locked, unreamed intramedullary nails. *J Orthop Trauma.* 1994; 8:45-9.
- Tornetta P 3rd, Bergman M, Watnik N, Berkowitz G, Steuer J. Treatment of grade-IIIB open tibial fractures: a prospective randomised comparison of external fixation and non-reamed locked nailing. *J Bone Joint Surg [Br].* 1994; 76:13-19.
- Tu YK, Lin CH, Su JI, Hsu DT, Chen RJ. Unreamed interlocking nail versus external fixator for open type III tibia fractures. *J Trauma.* 1995; 39:361-7.
- Bach AW, Hansen ST Jr. Plates versus external fixation in severe open tibial shaft fractures: a randomized trial. *Clin Orthop.* 1989; 241:89-94.
- Weitz-Marshall AD, Bosse MJ. Timing of closure of open fractures. *J Am Acad Orthop Surg.* 2002; 10:379-84.
- Gopal S, Majumder S, Batchelor AG, Knight SL, De Boer P, Smith RM. *et al.* Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. *J Bone Joint Surg Br.* 2000; 82(7):959-66.
- Cole JD, Ansel LJ, Scharzberg RA. sequential protocol for management of severe open tibial fractures. *Clin Orthop.* 1995; 315:84-103.