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Functional outcome of closed complex tibial plateau fractures treated using dual plating

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Abstract
Background: The tibial plateau fractures represent 1 to 2% of all fractures and approximately 8% of the fractures in elderly. Schatzker type V and VI tibial plateau fracture include Complex bicondylar injuries. The literature pertaining to functional outcome of closed bicondylar tibial plateau (Schatzker type V and VI) fractures treated using dual plates as internal fixation are scant.
Material and Methods: A prospective study was undertaken in a Tertiary Hospital from April 2017 to June 2019, 30 cases of closed proximal tibia classified as Schatzker's type V and VI fractures (bicondylar tibial plateau fractures) were managed surgically. The patients were followed up at 2nd, 6th, 12th and 24th postoperative weeks.
Results: Average oxford score was 38.5 ± 6.19, maximum (73.3%) of the patients had the score more than 40. The proportion of people having high oxford score was statistically significant (χ^2 =33.9, $p<$ 0.0001).
Conclusion: We conclude that open reduction and internal fixation using dual plates, is an excellent method of treatment of closed bicondylar tibial plateau (Schatzker type V and type VI) fractures in judiciously selected cases and we recommend the same.

Keywords: Schatzker type V and VI tibial plateau fracture, oxford score, dual plates

Introduction
The tibial plateau fractures represent 1 to 2% of all fractures and approximately 8% of the fractures in elderly. Industrialization and the acceleration of travel have resulted in increase in road traffic accidents which was associated with increase in the number of tibial plateau fractures [1].

Schatzker type V and VI tibial plateau fracture include Complex bicondylar injuries with significant articular depression, multiple displaced condylar fracture lines, metadiaphyseal fracture extension and comminution. Owing to high velocity trauma, they may be with open wounds or closed injuries with soft tissue injury. The severity of soft tissue injury and the degree of bone comminution reflects the energy transmitted to the bone and incline to unfortunate prognosis [2, 3].

The principles and techniques of treating tibial plateau fractures have evolved dramatically over the past 50 years. Many treatment modalities have been proposed for bicondylar tibial plateau fractures such as dual plate fixation, hybrid external fixation or Ilizarov external fixator.

Most patients have unsatisfactory clinical results with significant residual dysfunction even after the completion of treatment and have been associated with wound complications [4, 5]. Hence, the optimal treatment of Schatzker type V and VI tibial plateau fractures is still controversial and challenging, in the absence of standard, specific and proven treatment protocol [6].

In modern era of industrialization, optimal treatment with minimal hospital stay, early mobilization and minimal functional deficit has become the need of hour. Hence, operative treatment seems appropriate to avoid physical, social and psychological complications as well as prolonged immobilization. Modern operating techniques focus on the maintenance of the integrity and vascularity of the injured soft tissue to lessen the morbidity.

Current treatment options for bicondylar tibial plateau fractures include temporary plaster slab application, temporary external fixation prior to definite fixation, fine wire fixators like Ilizarov circular fixator or Taylor spatial frame, dual column plating and more recently arthroscopically assisted reduction and internal fixation with plating [7, 8].

External fixation using Ilizarov circular fixator or Taylor spatial frame allows early weight bearing without limitations related to skin condition and is preferred modality of treatment in cases with extensive bony comminution, bone loss, severe soft tissue injury and compound fractures [9, 10]. However, these fixators are associated with complications related to inadequate reduction, pin tract infection, deep infection. Various authors have reported surgical site infection rates related to pin tract infection as 9.1- 20% in their studies [11, 13]. Moreover, external fixators must be maintained until sufficient healing has occurred, which makes patient's acceptance and compliance difficult.

Open reduction and internal fixation using dual plating for bicondylar tibial plateau fractures has been proposed since the initial recommendation by Schatzker [14]. Dual plating provides rigid anatomic fixation for the articular components allowing early mobilization [15]. Over the years, concepts in dual plating have evolved from single incision to double incision technique, reporting lower wound complication rate and lesser adverse effects [16]. Variety of implants like conventional buttress plates, locking compression plates and angle stable plates are available which provide adequate stability in a severely comminuted or osteoporotic environment. These bio friendly implants can be used in various combinations like dual conventional buttress plating or dual LCP plating or lateral-LCP/medial-buttress dual plating or single-lateral LISS/LCP with or without lag screw fixation [17]. In terms of construct stability and reduction loss, no significant difference between LCP/buttress and conventional double buttress fixation has been reported [16]. Dual plating, hybrid or conventional, has reported satisfying results with minimal postoperative malreduction and non-union in recent studies [5].

Dual plating for complex bicondylar tibial plateau (Schatzker type V and VI) fractures has gained popularity because of its optimal functional outcome and patient compliance. Many studies have supported the use of this technique in complex bicondylar tibial plateau citing excellent functional outcomes and better patient compliance [15, 18, 19]. But still this modality is in evolving phase to improve patient outcome.

This prospective study aims to evaluate functional outcome of closed bicondylar tibial plateau (Schatzker type V and VI) fractures treated using dual plates as internal fixation.

Aims and Objectives

1) To study the functional outcome of closed bicondylar tibial plateau (Schatzker type V and VI) fractures using dual plates as internal fixation.
2) To study complications of dual plating in closed bicondylar tibial plateau (Schatzker type V and VI) fractures.
3) To study radiological outcome of closed bicondylar tibial plateau (Schatzker type V and VI) fractures using dual plates as internal fixation.

Materials and Methods

A prospective interventional study was done in the Department of Orthopaedics in Post Graduate Institute of Swasthiyog Pratishthan, Dr G. S. Kulkarni Fracture and Orthopaedic Hospital, Miraj Maharashtra between April 2017 to June 2019, 30 cases of proximal tibia classified as Schatzker's type V and VI fractures (bicondylar tibial plateau fractures) managed surgically, were included in the study after obtaining informed, written and video consent. Clearance from the institutional ethics committee was obtained before starting of the study.

Inclusion criteria

- All patients above 18 years of age with proximal tibia fractures radiologically classified as Schatzker's type V and VI fractures (bicondylar tibial plateau fractures) managed surgically.
- Closed tibial plateau fracture with or without skin abrasions or contusion.

Exclusion criteria

- Age less than 18 years.
- Tibial plateau fractures of Schatzker types I, II, III, and IV.
- Open fractures.
- Pathological fractures.
- Fractures with associated ipsilateral lower limb fractures or associated spine or pelvic fractures or patients with associated head injury.
- Fractures with neurovascular injury.
- Patients medically unfit for surgery.

Methodology

In the proposed study patients with closed bicondylar tibial plateau (Schatzker type V and VI) fracture were admitted to hospital, all the necessary clinical details were recorded in the proforma prepared for this study. All the patients were given preliminary management by temporary above knee POP slab and required medical management. The patients were taken for definitive fixation after a variable period of time till swelling subsided and skin condition improved. Definitive fixation was done in the form of medial and lateral column fixation by plates. Intra operative data were recorded. After the completion of the hospital treatment, patients were discharged and called for follow up at outpatient level, at regular intervals at 2, 6, 12 and 24 weeks.

In each determined follow up, clinical assessment of range of motion, radiological evaluation as by parameters i.e. medial proximal tibial angle, posterior proximal tibial angle and progression of healing (union; determined by visibility of fracture lines) was documented. Complications like surgical site infection, deep infection, knee stiffness, knee instability were documented. The Functional evaluation as done by patient on the basis of Oxford Knee Scores questionnaire at the end of 6 months of follow up was also documented.

Statistical method

Statistical analysis was done by using Microsoft Excel and IBM SPSS Statistics - 23. The data was summarized using percentages, mean and standard deviation. Difference in distribution of cases was analyzed using chi square test of goodness of fit. Chi square test of association was used to study association of qualitative data such as type and category of oxford score and range of motions. Difference in average final outcome in terms of MPTA and PPTA with respect to range of motion was studied using unpaired t test at 95% confidence interval. Pearson's Correlation coefficient was used to study correlations of age and oxford score, final range of motion and final radiological outcome in terms of PPTA.

Observation and Results

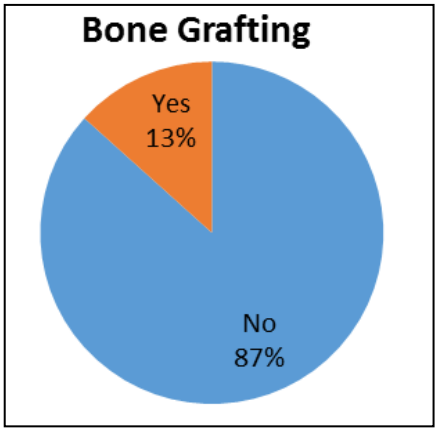
Table 1: Demographic data of the study group

Parameter		No. Of patients	Percentage (%)
Age	<=20	2	6.67
	20-30	13	43.33
	30-40	8	26.67
	>40	7	23.33
	Total	30	100.00
Sex	Male	28	93%
	Female	2	7%
	Total	30	100%
Mode of Injury	RTA	24	80
	PH	4	13.3
	FFH	2	6.7
	Total	30	100
Side affected	Right	16	53.33
	Left	14	46.67
	Total	30	100
Schatzker type	V	10	33.33
	VI	20	66.67
	Total	30	100
Time interval for surgery	1	1	3.33%
	1-5	8	26.67%
	5-7	8	26.67%
	7-10	4	13.33%
	10-15	7	23.33%
	>15	2	6.67%
	Total	30	100.00%

In our study, age of the patients was ranged from 19 yrs to 50 yrs. Mean age was 31.73 ± 8.2 years. In our study, there were 28 (93%) males, and 2(7%) females. The proportion of male patients was significantly higher than female patients (χ^2 = 22.53, p value <0.0001). The most common mode of injury observed in our series was road traffic accident. It accounted for 24 patients (80%).The next common cause was history of pedestrian hit accounting for 4 patients (13.3%) while history of fall from height was least prevalent (6.7%). The difference in mode of injury was statistically significant. (χ^2= 29.6, p value <0.0001) Out of 30 patients, 16 had injury on the right side while remaining 14 had on left side. The difference was not significant. (χ^2= 0.13, p value =0.94).

10 patients had Schatzker type V injury while the remaining 66.67% patients had Schatzker type VI injury. The difference was statistically not significant (χ^2= 3.47, p value =0.18).

The time interval between injury and definitive surgery was ranged from l day to maximum of 16 days**.** Average time between injury and surgery was 6.9 days.



Graph 1: Distribution of the study group according to requirement of bone grafting

Bone grafting was not required in 26 cases (86.6%). Thus significantly less number of cases required bone grafting (χ^2=16.l, p<0.0001).

Table 2: Intraoperative details of the study group

Parameter		No. Of patients	Percentage (%)
Blood Loss	<=110	1	3.33
	110-159	14	46.66
	160-209	11	36.66
	>=210	4	13.33
	Total	30	100.00
Duration of surgery	<120	5	16.67
	120-130	3	10.00
	130-140	8	26.67
	140-150	4	13.33
	150-160	5	16.67
	>160	5	16.67
	Total	30	100.00

Average blood loss was 162.8 ± 41.97 ml. It was observed that 46.66% of the patients had blood loss between 110-159 ml (χ^2= 0.0059, p value =0.999879).

Minimum time duration of surgery was 110 min and maximum was 170 min. Average duration of surgery was 139.7 min ± 17.6 min. The cases were almost equally distributed with respect to duration of surgery and the difference was statistically not significant (χ^2 = 2.8, p value = 0.42).

Table 3: Distribution of the study group according to Time for union.

Time taken for union (weeks)	No. Of patients	Percentage (%)
10-12	2	6.67
12-15	16	53.33
15-20	11	36.67
>20	1	3.33
Total	30	100.00

The average time for union was 14.37 weeks ± 3.4l weeks. Except 1 case which required 30 weeks. The Difference was statistically significant (χ^2=17.84, p value =0.0004).

Table 4: Distribution of the study group according to Complication

Complications	No of patients	Percentage
Nonunion (NU)	1	3.33
Superficial infection (SI)	5	16.67
Knee instability (KI)	1	3.33
Deep infection (DI)	1	3.33
None	22	73.33
Total	30	100

Significantly high (73.33%) of the cases did not have any complications (χ^2 = 55.3, p< 0.00001).

Table 5: Distribution of the study group according Oxford score

Oxford score	No of patients	Percentage
0-19	1	3.33
20-29	4	13.33
30-39	3	10.00
40-49	22	73.33
Total	30	100.00

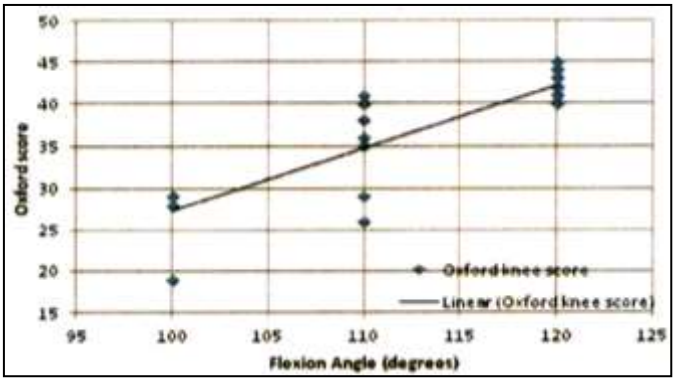
Average oxford score was 38.5 ± 6.19, maximum (73.3%) of the patients had the score more than 40. The proportion of people having high oxford score was statistically significant (χ^2 =33.9, p< 0.0001).

Table 6: Distribution of the study group according Association of range of motion and final radiological outcome.

Final flexion	MPTA		PPTA	
	Range	Mean± SD	Range	Mean± SD
100	83-87	85.4 ± 2.08	73-78	76.0 ± 2.6
110	84-91	87.3 ± 2.29	76-86	81.2 ± 3.3
120	83-92	87.0 ± 2.57	75-85	79.8 ± 2.9

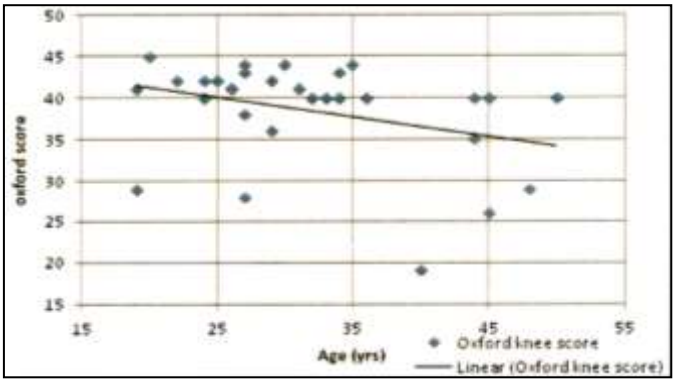
It was observed that average radiological outcome did not change with respect to angle of flexion. Association of final radiological outcome was also studied using Pearson's correlation coefficient.

Accordingly range of motion and MPTA were positively correlated with Pearson's correlation coefficient (r = 0,124, p<0.05). Similarly range of motion and PPTA were positively correlated with Pearson's correlation coefficient (r = 0.202, p< 0.0001).



Graph 2: Association of range of motion and Oxford score

It was observed that number of cases in different categories of oxford scores did not differ with change in flexion angle. However, analysis to find correlation between range of motion and oxford score revealed that the range of motion and oxford scores are positively correlated with Pearson's correlation coefficient (r = 0.82). The correlation was highly significant (t=7.5, p<0.0001).



Graph 3: Association of oxford score with age of patient

Data was analyzed to find correlation between age of patients and functional oxford score, using Pearson's correlation coefficient. It was observed that age of patients and oxford score are negatively correlated with Pearson's correlation coefficient (r= -1.91) i.e. oxford score decreases with increase in age. However the correlation was not statistically significant.

Discussion

The optimal treatment of complex bicondylar tibial plateau fractures (Schatzker type V and VI) is controversial. Literature shows mixed evidences favoring different method of treatment. Each of the surgical methods described have specific advantages and potential complications that must be appreciated by the treating surgeon. Achieving anatomical union within optimal time frame, early mobilization with better patient compliance and minimal complications are the main goals of a treatment strategy. The results of our study are comparable with the various studies conducted in India and other parts of the world.

Age distribution

In our study, mean age was 31.73 ± 8.2 years. In Khatri *et al.* study mean age was 42.98 years [19] and in Yao *et al.* study mean age was 43 years [5]. In Pun *et al.* study mean age was 43.85 years [6] and in Prasad *et al.* mean age was 40 years [15].

Sex distribution

In our study there were 28 (93%) males. In Biggi *et al.* study 67% patients were male [20] while in Manidakis *et al.* study 42% patients were female [21]. In Rademaker *et al.* study 44% patients were female [3] while in Tscherne *et al.* 55% patients were male [22]. This higher ratio can be explained by a higher involvement of males in outdoor activities, hence more vulnerable to vehicular accidents.

Mode of injury

In our study the commonest mechanism of injury was road traffic accidents in 80% of the patients. Manidakis *et al.*. reported the most common mechanism of injury were motor vehicle accidents 69% [21], Rademaker *et al.* reported most common cause was by RTA, i.e. in 53% of the cases [3]. Lansinger *et al.* reported 33% due to fall from height and 36% fall from level surface [23].

Functional outcome

In our study 73.33% of patients had oxford score 40 - 49 while Khatri *et al.* study reported oxford score of 40 - 49 in 83% of their patients [19]. While Prasad *et al.* reported 40% patients had oxford score 40 - 49 [15].

Time interval between injury and definitive surgery

In our study time interval between injury and definitive surgery was 1 to 16 days. In a study by Pun *et al.* this time interval ranged from 12 hours to 21 days [6] while Yao *et al.*, in their study reported time interval of 7 - 14 days [5]. Khatri *et al.*, in their study stated that majority of patients were operated within 14 days [19].

Complication

In our study superficial infection was reported in 16.67% of patients while deep infection was in 3.33% of patients. In a study by Khatri *et al.* superficial wound infection was seen in 9.2% patients while deep infection was seen in 4.6% of patients [19]. In a study by Ozkaya *et al.*, superficial infection was seen in 13.63% while deep infection was seen in 4.54% of patients [24]. In 2006, a multicenter, prospective, randomized control trial by Canadian Orthopaedic Trauma Society (COTS) reported an overall infection rate of 18% in bicondylar tibial plateau fractures treated with open reduction and internal fixation [25].

Fracture union

In our study except one case, all cases showed union. One case went into non-union. In a study by Bhavani Prasad *et al.*

all cases showed union [26]. In a study by Yao et.al out of 74 patients of bicondylar tibial plateau fractures, 62 showed union, and 12 patients went into delayed union while no case of non-union was reported [5]. In a study by Prasad *et al.*, all patients showed union [15].

Association between age of patient and functional outcome evaluated using oxford score

It was observed that age of patients and oxford score are negatively correlated (r=-1.91) i.e. oxford score decreases with increase in age. However
the correlation was not statistically significant. Yao *et al.* and Khatri *et al.* also did not find association between oxford score and age of patient [5, 19].

Conclusion

In our study, Good to Excellent outcome was seen in 83.3% of the patients, of an average age of 31.73 years, with closed bicondylar tibial plateau (Schatzker type V and VI) fractures according to Oxford Knee Score, at the end of 6 months.

Hence, we conclude that dual plate technique with dual incisions provides good fixation for closed bicondylar tibial plateau (Schatzker type V and VI) fractures if proper preoperative planning and surgical techniques are followed, leading to high rate of bone union and minimal soft tissue damage. Therefore, it allows early aggressive knee mobilization that in turn enhances the process of union, avoids knee stiffness and goes a long way in ensuring optimal functional recovery and patient satisfaction. Most of the complications of dual plate technique are related to soft tissue problems, operative technique, type of fracture, physiotherapy, instruments and implant quality which can be brought down by proper preoperative planning.

Dual Plate technique requires a higher surgical skill, proper positioning of the patient, adequate exposure, good instrumentation and vigilant mobilization in the form of physiotherapy. The implants are comparatively expensive and it has a steep learning curve. Therefore, should be used after proper training.

In conclusion, open reduction and internal fixation using dual plates, is an excellent method of treatment of closed bicondylar tibial plateau (Schatzker type V and type VI) fractures in judiciously selected cases and we recommend the same.

Limitations in this study

Finally, our study has certain limitations including lack of control group, short follow-up period and less number of cases. The limited number of cases may decrease statistical power as well as our ability to analyze the results. More complications may appear over a longer follow-up period.

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Conflicts of Interrest: Nil

References

1. JR L, DJ J, GJH. Tibial plateau fractures. In: Scott WN, Insall TN, editors. Insall & Scott Surgery of the Knee. 5 ed: Churchill Livingstone 2012, 773-85.
2. Dirschl DR, Dawson PA. Injury severity assessment in tibial plateau fractures. Clin Orthop Relat Res 2004(423):85-92.
3. Rademakers MV, Kerkhoffs GM, Sierevelt IN, Raaymakers EL, Marti RK. Operative treatment of 109 tibial plateau fractures: five- to 27-year follow-up results. J Orthop Trauma 2007;21(1):5-10.
4. Mckee PS, Stephen DJ. The Canadian Orthopedic Trauma Society. Open reduction and internal fixation compared with circular fixator application for bicondylar tibial plateau fractures. Results of a multicenter, prospective, randomized clinical trial. J Bone Joint Surg Am 2006;88(12):2613-23.
5. Yao Y, Lv H, Zan J, Li J, Zhu N, Jing J, *et al.* Functional outcomes of bicondylar tibial plateau fractures treated with dual buttress plates and risk factors: a case series. Injury 2014;45(1-2):1980-4.
6. Pun TB, Krishnamoorthy VP, Poonnoose PM, Oommen AT, Korula RJ. Outcome of Schatzker type V and VI tibial plateau fractures. Indian J Orthop 2014;48(1):35-41.
7. Zura RD, Browne JA, Black MD, Olson SA. Current management of highenergy tibial plateau fractures. Current Orthopaedics 2007;21(3):229-35.
8. Burdin G. Arthroscopic management of tibial plateau fractures: surgical technique. Orthop Traumatol Surg Res 2013;99(1):S208-18.
9. Dendrinos GK, Kontos S, Katsenis D, Dalas A. Treatment of high-energy tibial plateau fractures by the Ilizarov circular fixator. J Bone Joint Surg Br 1996;78(5):710-7.
10. Catagni MA, Ottaviani G, Maggioni M. Treatment strategies for complex fractures of the tibial plateau with external circular fixation and limited internal fixation. J Trauma 2007;63(5):1043-53.
11. Kataria H, Sharma N, Kanojia RK. Small wire external fixation for high-energy tibial plateau fractures. J Orthop Surg (Hong Kong) 2007;15(2):137-43.
12. Ali AM. Outcomes of open bicondylar tibial plateau fractures treated with Ilizarov external fixator with or without minimal internal fixation. Eur J Orthop Surg Traumatol 2013;23(3):349-55.
13. Hutson JJ Jr, Zych GA. Infections in periarticular fractures of the lower extremity treated with tensioned wire hybrid fixators. J Orthop Trauma 1998;12(3):214-8.
14. Schatzker J, McBroom R, Bruce D. The tibial plateau fracture. The Toronto experience 1968-1975. Clin Orthop Relat Res 1979(138):94-104.
15. Prasad GT, Kumar TS, Kumar RK, Murthy GK, Sundaram N. Functional outcome of Schatzker type V and VI tibial plateau fractures treated with dual plates. Indian J Orthop 2013;47(2):188-94.
16. Zhang Y, Fan DG, Ma BA, Sun SG. Treatment of complicated tibial plateau fractures with dual plating via a 2-incision technique. Orthopedics 201 2;35(3):e359-64.
17. Perren SM. The technology of minimally invasive percutaneous osteosynthesis V (MIPO). Injury 2002;33(1):6-7.
18. Hassankhani EG, Kashani FO, Hassankhani GG. Treatment of Complex Proximal Tibial Fractures (TypesV & VI of Schautzker Classification) by Double Plate Fixation with Single Anterior Incision. Open Journal of Orthopedics 2013;3(04):208.
19. Khatri K, Lakhotia D, Sharma V, Kiran Kumar GN, Sharma G, Farooque K, *et al.* Functional Evaluation in High Energy (Schatzker Type V and Type VI) Tibial Plateau Fractures Treated by Open Reduction and Internal Fixation. International Scholarly Research Notices 2014;2014:8.
20. Biggi F, Di Fabio S, D'Antimo C, Trevisani S. Tibial

plateau fractures: internal V fixation with locking plates and the MIPO technique. Injury 2010;41(11):1178- 82.
21. Manidakis N, Dosani A, Dimitriou R, Stengel D, Matthews 5, Giannoudis P, *et al.* Tibial plateau fractures: functional outcome and incidence of osteoarthritis in 125 cases. Tnt Orthop 2010;34(4):565-70.
22. Tscherne H, Lobenhoffer P. Tibial plateau fractures. Management and expected results. Clin Orthop Relat Res 1993(292):87-100.
23. Lansinger, Bergman B, Korner L, Andersson GB. Tibial condylar fractures. A twenty-year follow-up. J Bone Joint Surg Am. 1986;68(1):13-9.
24. Ozkaya U, Parmaksizoglu AS. Dual locked plating of unstable bicondylar tibial plateau fractures. Injury 2015;46(2):S9-13.
25. Canadian Orthopaedic Trauma S. Open reduction and internal fixation compared with circular fixator application for bicondylar tibial plateau fractures. Results of a multicenter, prospective, randomized clinical trial. J Bone Joint Surg Am 2006;88(12):2613-23.
26. Prasad TB, Reddy BS, Vennala B, Kumar TD, Nalla S. A clinical study on surgical management of tibial plateau fractures-functional and radiological V evaluation. Journal of Evidence based Medicine and Healthcare 2015;2(43):7737-52.