Study and Analyses Plan

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Are tibial plateau fractures associated with an increased risk of early knee arthroplasty? A matched cohort study of X000[1] tibial plateau fractures with an average of XX[1] years follow-up

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[1] The average follow-up period and number of patients will be calculated when data is available.

Background

Fractures of the proximal articular surface of the tibia are rare and constitutes approximately 1% of all fractures[1]. A recent study by Elsoe et al. [2] reported an overall incidence of 10.3/100,000/year, with increasing incidence with increasing age. Elsoe et al. [2] reported that both genders have the highest frequency of tibial plateau fracture between the ages of 40 and 60 years.

The long-term outcomes following fractures of the tibial plateau are associated with increased risk of knee pain, joint stiffness, malalignment, symptomatic hardware, arthrofibrosis, posttraumatic arthritis and limitations in activity of daily living and quality of life[3–12].

Traumatic knee injuries may increase the risk of later development of post-traumatic knee arthritis. Intra articular fractures of the knee joint is considered to be a major risk factor in the development of post-traumatic osteoarthritis[13]. Brown et al. [14] estimated that approximately 12% of all patients with symptomatic osteoarthritis of the hip, knee or ankle joint are due to post-traumatic osteoarthritis. Factors such as the force applied to the chondral surfaces during injury, fracture comminution, mode of injury, older age, female gender, comorbidity, the quality of articular reduction and treatment methods, have all been suggested to influence the risk of developing post-traumatic osteoarthritis following a tibial plateau fracture [15–18]. The incidence of post-traumatic osteoarthritis following a tibial plateau fracture is reported with wide ranges from 21-45% [7, 15, 17, 20–23].

In general, total knee arthroplasty (TKR) is a highly successful procedure in the treatment of end-stage knee osteoarthritis[18, 24, 25]. However, most authors reported outcomes of TKR in patients with a previous tibial plateau fracture were associated with worse outcome and increased complications[26–29] compared to TKR following primary osteoarthritis of the knee.

In a series of 8426 patients with a previous tibial plateau fracture all treated by open reduction and internal fixation (ORIF) Wasserstein et al. [18] reported that 7.3% of patients had received a TKR 10 years after fracture. This corresponded to a 5.3 times increased likelihood of receiving a TKR compared to a matched reference group from the general population[18]. However, Wasserstein et al. [18] did not include side specific observations of the correlation between tibial plateau fractures and TKR, which excludes the possibility to estimate the ipsilateral and contralateral incidences. Moreover, Wasserstein et al. [18] did not provide secondary outcome

regarding other surgical procedure well known in the treatment of knee osteoarthrosis such as knee arthroscopy and realignment osteotomy. Mehin et al.[13] studied 311 patients with a previous tibial plateau fracture and reported that 4% had major reconstruction surgery, including TKR and 13% had undergone arthroscopy or injection of the knee joint at an average of 10-years follow-up. Moreover, Rademakers et al. [16] evaluated 109 patient with an average of 14 years follow-up and reported a 5% incidence of reconstructive surgery following a previous tibial plateau fracture.

To the authors knowledge the literature lacks long-term adequately powered studies with the aim to systematically examined the association between a tibial plateau fracture and subsequent treatment with either TKR, realignment osteotomy or arthroscopic procedures.

The primary aim of the study is to report the cumulative incidence of ipsilateral TKR at xx years following tibial plateau fractures and compare this to the cumulative incidence of ipsilateral TKR in an age and gender matched non-exposed group without a prior tibial plateau fracture.

The secondary aim of the study is to report the cumulative incidence of ipsilateral arthroscopy, realignment osteotomy, contralateral TKR and contralateral arthroscopy of the knee at xx years following a tibial plateau fracture compared to the cumulative incidence of ipsilateral arthroscopy, realignment osteotomy, contralateral TKR and contralateral arthroscopy of the knee in an age and gender matched non-exposed group without prior tibial plateau fractures. Furthermore, the third aim of the study is to compare the time to ipsilateral and contralateral TKR, realignment osteotomy and arthroscopy of the knee following a tibial plateau fracture compared to that of an age and gender matched non-exposed group.

The primary hypothesis of the study is that the cumulative incidence after xx years of ipsilateral TKR following a tibial plateau fracture is higher compared to an age and gender matched non-exposed group without prior tibial plateau fractures.

Patients and methods

The study is designed as a matched cohort study. All patients who sustained a tibial plateau fracture in Demark between the 1th. January 1996 and the 31th. of December 2000, are included as exposed and followed until 2015 with regards to development

of posttraumatic osteoarthritis requiring treatment in terms of TKR, realignment osteotomy or arthroscopic procedures.

The primary outcome is ipsilateral TKR (yes/no) within the follow-up period. The secondary outcomes are ipsilateral arthroscopy and realignment osteotomy of the knee (yes/no) and contralateral TKR/arthroscopy of the knee.

The study is undertaken in Denmark, which has a population of 5,699,220 as of December 31th. 2015. Danish law requires that all patient contacts with hospital and outpatient clinics in Denmark are registered in the Danish National Patient Registry(LPR)[30]. The Civil Registration Number is given to all residents of Denmark and registered in the Civil Registration System. Hospital identification, date and time of activity, and patient's municipality (among other characteristics) are registered[31]. This system enables researchers a complete registration of all health-related issues on an individual- and population-based level.

The exposed group is conducted with a retrospective review of all patients diagnosed with a tibial plateau fracture between the 1th of January 1996 and 31th. of December 2000. All patients are followed from the time of tibial plateau fracture until 2015 with regards to surgery with TKR, realignment osteotomy or arthroscopic surgery of the knees. Patients are censored in case of emigration from the country. Death and receiving a TKR on the side of the tibial plateau fracture is considered a competing event.

The non-exposed group will consist of individuals identified from the Civil Registration System matched to the exposed group on age (year of birth) and gender. For each exposed 10 non-exposed are selected who had not experienced a tibial plateau fracture on the same side as the injured knee of the corresponding exposed patient on the date of the fracture. Non-exposed are hence considered side-specific. Both exposed and non-exposed are censored in case of emigration from the country or at the end of follow-up.

This study is conducted in accordance with the ethical standards of the responsible committee and with the ethical principles of the 1975 Declaration of Helsinki. The Local Ethics Committee was asked to approve the study and answered the study design does not need notification. The study is approved by the Danish Data Protection Agency (J. nr. 2008-58-0028, Id: 2016-176). The reporting of the study

complies with the ` The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement [32].

Data retrieval

All patients who are registered regardless of contact type with the ICD-10 diagnose code tibial plateau fracture (DS82.1) between the 1th of January 1996 and 31th. of December 2000 are identified in the LPR (Danish National Patient Registry) and basic characteristics; age, gender, age at the time of diagnose and side of fracture is obtained (exposed). Patients are included at the time of first contact with a tibial plateau fracture in the LPR. Patients with prior tibial plateau fractures and patients with prior TKR are excluded from the study. Side specific information about TKR, realignment osteotomy, arthroscopy and tibial plateau fractures are then obtained from the LPR if occurred between the time of inclusion and 31th. of December 2015.

All identified patients with a tibial plateau fracture are matched by age (year of birth), gender, side of fracture at the time of fracture with a ratio of 1 to 10 from the CPR (Civil registration number) (non-exposed) and specifically matched to the exposed on the fracture date. Non-exposed with TKR or tibial plateau fracture on the same side as the matched exposed prior to the inclusion date are excluded (LPR). Non-exposed are identified in the LPR regarding surgery related to arthroscopy of the knees, realignment osteotomy, TKR and tibial plateau fracture from the date of inclusion until 31th. December 2015.

Statistics

Baseline characteristics of the study population will be reported in a descriptive table with separate information for the two groups. This will include medians and interquartile ranges for continuous variables and frequencies and percentages for categorical variables.

The primary outcome is the cumulative incidence reported yearly in the entire observational period of ipsilateral TKR in the two groups. We will estimate the relative difference between the two groups yearly during the entire observational period. Death will be considered as a competing event.

The time to event will be counted from the date of tibial plateau fracture diagnosis for the exposed group and the corresponding matching date for population non-exposed. Event times will be censored at the date of emigration from the country or end of the study follow-up by 31th of December 2015 and death will be considered as a competing event. We will perform the analysis evaluating the effect of tibial plateau fracture on ipsilateral TKR using a Cox proportional hazards regression model comparing exposed to non-exposed. We will report the effect estimate from this analysis as a hazard ratio with corresponding 95% confidence interval to estimate the incidence rate ratio. We will report results from the crude analysis without adjustments. Furthermore, we will repeat the analysis stratified by age-groups (0-50, 51+) and gender. To investigate the assumption of proportional hazards we will divide the follow-up time into 1-year periods.

We will perform additional analyses to investigate the effect of tibial plateau fracture on the secondary outcomes (ipsilateral and contralateral arthroscopy of the knees, ipsilateral realignment osteotomy and contralateral TKR) following the same methods as for the main analysis except that we will also consider TKR as a competing event for arthroscopy in the same side.

All analyses will be performed using Stata statistical software (StataCorp LP) and the significance level for analyses (α) will be set to 0.05. All analyses will be performed by an experienced statistician.

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