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Microfracture of the Knee: Which Findings Can Be Derived From Statistical Analyses Summarizing 16 Studies?

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Abstract

Objective: To statistically summarize all available results presented in the literature; to compute an inherently meaningful best estimate of the mean expectable treatment effect; to provide statistical evidence that advanced age and large chondral lesions adversely effect the outcome after microfracture.

Methods: We searched four electronic databases for prospective and retrospective studies that included sufficient statistical information. In order to convert all score values to the most frequently used Lysholm Score a regression analysis had to be performed at first, using data of 26 own patients. Subsequently, meta-, subgroup and regression analyses were performed.

Results: 16 studies representing 777 patients aged from 13 to 72 years with chondral lesions from 0.2 cm² to 20 cm² of size, evaluated after a follow-up period of six to 17 years referred to our eligibility criteria. We calculated an overall best estimate of 26.76 Lysholm points for the mean treatment effect. With values of 22.38 Lysholm points for group 1 (patients younger than 38 years on average) and 31.11 Lysholm points for group 2 (patients with a mean age greater-than-or-equal to 38 years) our subgroup analysis revealed a barely significant difference between the two means (p=0.499). Due to the fact that the mean preoperative score value in group 2 was considerably lower than in group 1 these findings might be caused by the uneven increase of the Lysholm Score and not by age-related facts. However, neither a subgroup analysis referring to the defect size, nor a linear regression with mean age as the predicting variable could reveal significant results.

Conclusion: Our meta-analysis enables patients to take a realistic view on their improvement in quality of life after knee microfracture, but it does not facilitate surgeon's decision whether microfracture is the appropriate technique to treat a given full-thickness cartilage lesion of the knee.

Keywords: Microfracture of the knee; Meta-analysis; Subgroup analysis; Linear regression; Treatment effect; Best estimate

Introduction

Since 1980, Steadman has followed a minimal-invasive specific approach to treat full-thickness chondral defects of the knee [1] in order to "*recreate the structures of the knee that protect it from impact and provide stability*" [2]. Whereas it was applied only by about 1% of orthopedic surgeons worldwide in 1994, that statistic was up to 85% 10 years later [3]. It is estimated that today worldwide more than 500,000 patients per year are treated with this technique [4]. Unfortunately, studies have shown different and sometimes contradictory results with regard to the treatment effect and to outcome predicting factors. In order to combine these informations, we already performed a meta-analysis by synthesizing all available randomized controlled trials and cohort studies [5]. We calculated an overall best estimate of 1.106 with (0.566; 1.646) a 95% confidence interval, of the mean standardized treatment effect. Unfortunately, we could not convert the summarized effect back into the respective scales of the numerical scores because the standard deviations referring to the differences in the pre and postoperative score values were missing. Furthermore, neither subgroup analysis nor regression analysis could be performed due to the small number of controlled studies. Therefore, the objective of this paper was to provide a inherently meaningful (not standardized) best estimate of the avarage expected treatment effect by summarizing all available studies. Furthermore, we intended to provide statistical evidence that advanced age and large chondral lesions have a negative impact on the outcome after microfracture of the knee.

Materials and Methods

We searched the electronic databases MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials for prospective and retrospective studies providing mean and standard deviation or range of the outcome parameters. Our literature search was completed on September 1, 2011. As "microfracture" is the generally accepted notation for this technique, we decided to use it as our search term. No language restrictions were applied. Our eligibility criteria meet the requirements of the PICOTS [6,7] strategy, they are presented in (Tables 1 and 2).

Statistical analysis

Our analyses of continuous outcome data were performed according to Borenstein [8] and Schwarzer [9-11] and calculated with the package "meta" in the statistic program R [12] using the random effects model of Schwarzer et al. [11] for weighting the individual studies. The treatment effect, i.e. the difference between the mean pre- and postoperative Lysholm Score values, was appointed as effect size [13]. Score values referring to other outcome measures than the

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Population	Patients with full-thickness cartilage defects (Outerbridge grades III and IV) on the medial or lateral femoral condyle, the trochlea or the patella as a consequence of acute or repetitive trauma, osteonecrosis, or osteochondritis dissecans
Intervention	Microfracture (without implantation of a scaffold or injection of substitutes)
Control	Any active control group
Outcome	Functional capacity assessed with clinical scores
Timing	Studies with a minimum follow-up period of one year
Study design	Any prospective or retrospective study

Table 1: Eligibility criteria.

Study	Study design	Score	Mean score value pre (LP)	Patient number	Age	Defect size	Follow- up
Steadman 03	RCS	Lysholm	58.8	71	30.4	277.4	11.3
Miller 04	RCS	Lysholm	53.8	79	49.4	229.5	2.6
Sterett 04	RCS	Lysholm	43.5	33	51.3	N.R.	3.8
Akgun 05	RCS	mod. Lysholm	40.19	41	42.1	235.2	2.6
Gobbi 05	PCS	Lysholm	56.8	53	38	400	6.0
Gudas 05	RCT	IKDC	67.85	29	24.3	277	3.1
Marder 05	RCST	Lysholm	35.07	43	39.7	< 200	4.2
Alparslan 07	RCS	mod. Lysholm	68.21	20	44	130	3.8
Knutsen 07	RCT	Lysholm	55	40	31.1	450	2.0
Miller 07	RCS	Lysholm	49.9	61	52.2	N.R.	3.0
Taşer 07	RCST	Lysholm	48	13	33.3	217	4.1
Asik 08	RCS	Lysholm	54.2	90	34.5	199.24	5.7
Saris 08	RCT	KOOS	71.3	61	33.9	240	1.5
Kon 09	CS	IKDC	61.6	40	30.6	250	5.0
Solheim 09	PCS	mod. Lysholm	40.07	86	38.4	483	5.0
Basad 10	RCT	Lysholm	55	17	37.5	> 400	2.0

Table 2: Demographic data extracted from text, tables and graphs (RCS = retrospective case series, PCS = prospective case series, RCT= randomized controlled trial, CS = cohort study, RCST = retrospective comparative study, PCST = prospective comparative study, N.R. = not reported. LP = Lysholm points).

Lysholm Score [14] had to be transformed in Lysholm points initially, using regression equations that had been developed on the basis of 26 own patients at our Level I trauma center. Statistical heterogeneity was assessed by calculating the heterogeneity measure I^2 according to Higgins et al. [15]. The publication bias was graphically tested by funnel and radial plots [11]; additionally, tests for funnel plot asymmetry were performed. A sensitivity analysis was done to determine the robustness of the results. Furthermore, subgroup analyses referring to age and defect size were computed on the basis of the Q-test for heterogeneity [16] and a simple meta-regression according to Everitt and Hothorn [17] was performed with age as the independent variable.

Results

Out of 1,030 citations obtained from electronic literature search, 16 studies (Steadman et al. [18], Miller et al. [19], Sterett and Steadman [20], Akgun et al. [21], Gobbi et al. [22], Gudas et al. [23,24], Marder et al. [25], Alparslan et al. [26], Knutsen et al. [27,28], Miller et al. [29], Taşer et al. [30], Asik et al. [31], Saris et al. [32,33], Kon et al. [34], Solheim et al. [35] and Basad et al. [36]) referred to our eligibility criteria. They represented 777 patients aged from 13 to 72 years with chondral lesions from 0.2 cm^2 to 20 cm^2 of size, evaluated after a follow-up period of six to 17 years with the Lysholm and Gillquist [14], the modified Tegner and Lysholm [37] and the IKDC [38] Score as well as the KOOS [39]. The selection process of the studies is documented in a PRISMA Flow Diagram [7] (Figure 1); relevant demographic data are presented in (Table 1).

Figure 2 displays the results of our regression analyses. Of the five KOOS subscores, the KOOS ADL (activities of daily living) has proven to be the most suitable score to be converted to the Lysholm Score by regression equations. The respective regression line and the regression lines of the modified Lysholm and the IKDC Score are presented in scatter plots; the black squares indicate the data points referring to our 26 patients. By definition, the regression line allocates a Lysholm Score value to each value (measured in modified Lyshom points, IKDC points and KOOS ADL points, respectively) chosen on the horizontal axes. Once the outcome parameters had been transformed to a uniform scale they could be synthesized without standardization.

Our meta-analysis of 16 studies is visualized in a forest plot [40] (Figure 3). The mean treatment effect of each individual study is marked by a short vertical line plotted on a horizontal line that represents the 95% confidence interval; it's width is directly proportional to the variation of the data and indirectly proportional to the number of patients [41]. Furthermore, the size of the square indicates the weight that is given to the individual study for the calculation of the weighted mean; recognizable by the centre of the diamond with its width representing the relevant 95 % confidence interval. Due to the fact that the diamond does not cross the line of no effect (0 Lysholm points) the summary effect is significant [40]. Hence, 26.76 Lysholm points with (22.01; 31.51) a 95% confidence interval have to be considered as the best estimate of the average treatment effect that can be expected after knee microfracture ($p<0.0001$). However, the forest plot reveals a high heterogeneity of the individual studies which is confirmed by the heterogeneity measure $I^2=0.961$ ($p<0.0001$); 96.1% of the heterogeneity is based on differences between the studies and not on randomness [11]. Neither funnel and radial plot nor several statistical tests provided evidence of a publication bias, i.e. the tendency to publish a study based on the favourable or statistically significant results rather than on the basis of its theoretical or methodical quality [42]. Furthermore, a sensitivity analysis was performed; the weighted mean was not notably influenced by omitting single studies. Due to these findings, it has to

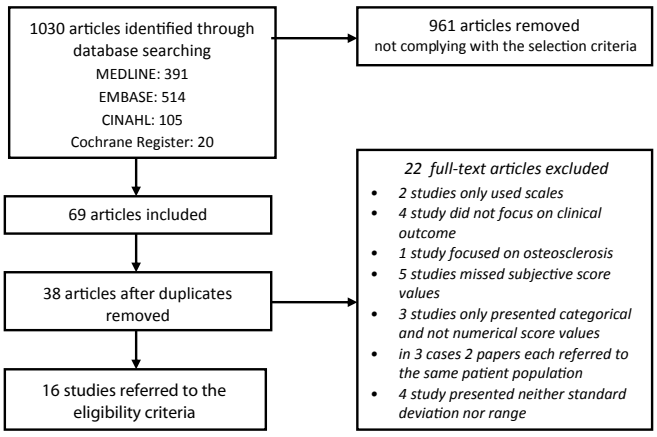

Figure 1: Selection process of eligible studies.

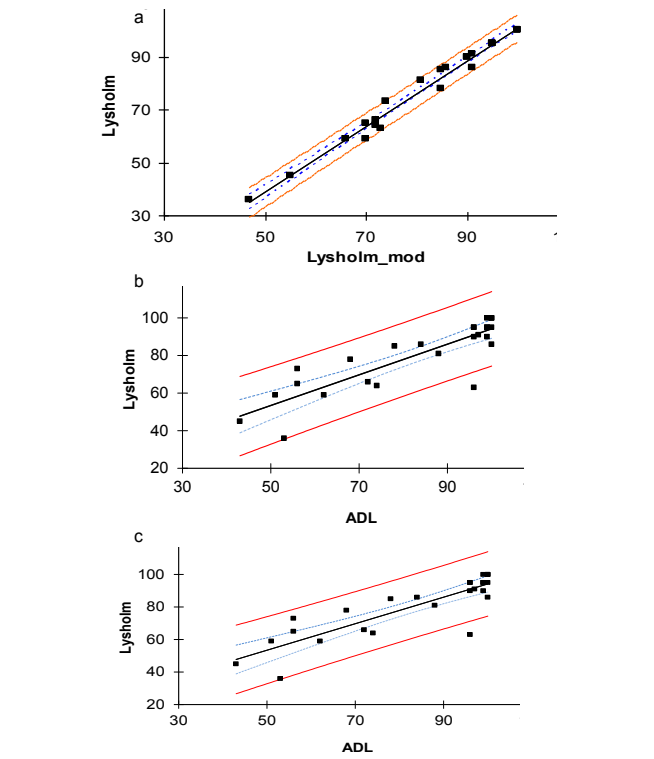

Figure 2: Significant regression line (p<0.0001) (black) with its 95% confidence interval (blue) and the 95% prediction interval for a single value referring to a) the modified Lyshom Score, b) the IKDC Score and c) the KOOS ADL as independent variable and the Lysholm Score as dependent variable.

be expected that patient- and defect-specific parameters like age and lesion size significantly influence the outcome after microfracture.

Figure 4 graphically displays the subgroup analysis according to patient age. Because large differences in sample sizes can cause problems in the analysis [43] we dichotomized by the median. Studies with patients younger than 38 years on average were coded as "1" and those with a mean age greater-than-or-equal to 38 years were coded as "2". Whereas group 1 showed a weighted mean of 22.38 Lysholm points with (16.07; 28.68) a 95% confidence interval, the accordant value for group 2 was 31.12 (25.07; 37.17) Lysholm points. Relying on commonly accepted benchmarks [44,45] the treatment effect was barely significantly higher (p=0.499) for the older patients.

Considering the lesion size, only 14 studies were available. Studies with a mean defect size less than 245 mm² (median) were coded as "1" and the others as "2". With weighted means of 22.63 with (16.07; 29.18) a 95% confidence interval for group 1 and 29.99 (22.35; 37.62) for group 2 no significant difference could be revealed (p=0.1764).

Finally, a linear regression was performed in order to provide a relationship between the mean treatment effect as dependent variable and the mean age as independent (explanatory) variable. The relevant scatter plot is presented in figure 5. The regression equation was computed to

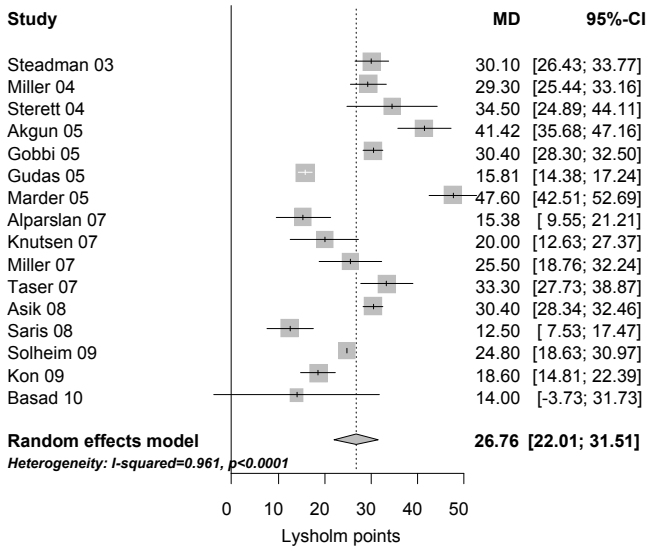

Figure 3: Forest plot.

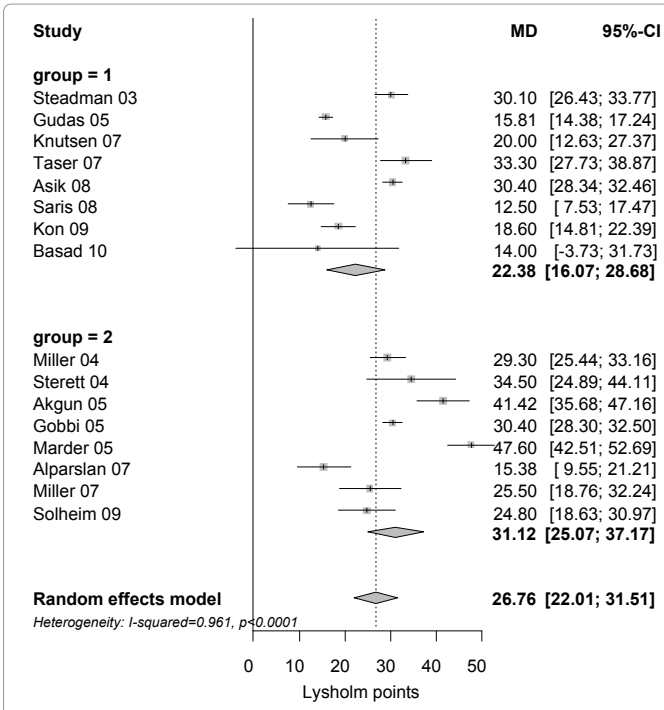

Figure 4: Subgroup analysis according to age.

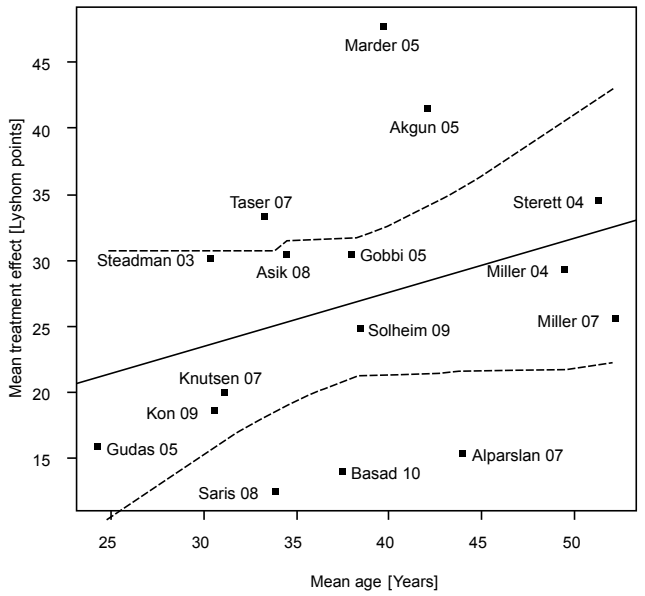

Figure 5: Scatter plot of mean age and mean treatment effect including the non-significant regression line and its 95% confidence interval.

mean treatment effect in Lysholm points = 0.4085 · mean age + 11.268

Which indicates the direct proportionality of mean age and mean treatment effect; or in other words, an increase of the mean age of one year induces an increase of the mean treatment effect of 0.4085 Lysholm points. Nevertheless, this relationship has to be considered coincidental because the relevant p-value was calculated to 0.213, meaning that the regression line is parallel to the age-axis. In consequence age cannot be considered a predictor variable of the treatment effect.

Discussion

Our meta-analysis computed a mean treatment effect of 26.76 Lysholm points. As an example, an improvement of two levels in the categories "instability" (10 Lysholm points), "pain" (10 Lysholm points) and "swelling" (5 Lysholm points) each as well as an improvement of one level in the category "limp" (2 to 3 Lysholm points) corresponds to this value. It reflects a considerable increase in patient`s quality of life. Therefore, 26.76 Lysholm points do not only represent a statistically significant but also a clinically significant value.

A systematic review identified age with a limit of 30 to 40 years and defect size with a limit of 2 cm^2 and 4 cm^2, respectively as outcome predicting factors [46]. Unfortunately, our analyses did not prove that small lesion size and low patient age have an adverse impact on the treatment effect achieved by knee microfracture. Surprisingly, our subgroup analysis even revealed a significantly higher treatment effect for group 2 which combined studies with a mean patient age of greater-than-or-equal to 38 years. This result contradicts not only to Mithoefer et al.'s findings [46] but also to common understanding [47,48]. It is generally accepted that the amount of proteins and the viscosity of the synovial liquid decline and the number of chondrocytes decreases starting at the fourth decade [48]. As the regeneration capacity of cartilage is reduced in older patients a repair tissue of inferior quality is formed after microfracture, resulting in lower postoperative score values [49]. However, this does not mean that the treatment effect has also to be expected lower because it represents an improvement referring to the starting point (i.e. the relevant preoperative score value). Due to the fact that the Lysholm Score values range from 0 to 100 points, the model of logistic growth – it is characterized by a quick increase at first and a slow approach to the upper limit afterwards – seems to be adequate to explain the result of our subgroup analysis. Thereby, the actual outcome (measured in fictitious units) is represented by the x-axis and the assigned score value by the y-axis. Whereas the same postoperative improvement provokes a high treatment effect when the preoperative score value is plotted on the exponential segment of the curve, it results in a small treatment effect when the patient already starts at a high preoperative value. Generally, it is more likely that older patients start at a lower preoperative score value than younger ones because low score values represent low functionality and distinct symptoms. Comparing the mean preoperative score values of group 1 (58.97 Lysholm points) and group 2 (48.44 Lysholm points) this assumption applies to our subgroup analysis. In consequence, the significant difference of the two treatment effects seems to be provoked rather by lower preoperative score values than by advanced patient age. Of interest, our linear regression could not identify age as a predicting factor, whereas Steadman et al. [18] computed a standardized regression coefficient of -0.299 (p=0.011), indicating that the mean treatment effect increases with decreasing mean age.

Limitations of our statistical analyses include the fact that four scores had been used for outcome evaluation. Therefore, in order to provide a clinically meaningful best estimate of the mean expectable treatment effect the differently measured outcome had to be converted to a uniform scale at first and estimates of some missing standard deviations had to be made. Furthermore, patients who needed a secondary surgery (failures) were handled in a different way by the respective authors. Whereas they remained in the study of Knutsen et al. [27] and Kon et al. [34] with their last recorded clinical follow up score before the failure considered to be their final clinical score [36], their data were excluded from the analysis by Steadman et al. [18] .

Conclusion

The mean expectable treatment effect provided by our meta-analysis allows patients to draw up realistic estimates of their achievable improvement of quality of life after knee microfracture. However, we could not provide limits referring to age and defect size that help surgeons in their decision whether microfracture is the appropriate technique to treat a given full-thickness cartilage lesion of the knee. Furthermore, we could not predict the treatment effect by patient age.

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