Is a high tibial osteotomy superior to non-surgical treatment in patients with varus malaligned medial knee osteoarthritis? A propensity matched study using 2 RCT datasets

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Abstract:

Objective:

No randomized controlled trial (RCT) has compared the high tibial osteotomy (HTO) with non-surgical treatment in patients with medial knee osteoarthritis and varus malalignment. The aim was to compare the effectiveness of an unloader brace treatment or a usual care program to the HTO regarding pain severity and knee function.

Design:

Surgical treatment (HTO) to two non-surgical options was compared by combining the data of two RCTs. One RCT (n=117) compared an unloader brace to usual care treatment; the other RCT (n=92) compared closing to opening wedge HTO.

One-to-many propensity score matching was used to equalize patient characteristics. We compared clinical outcome at 1 year follow-up (VAS pain (0-10) and knee function (HSS, 0-100)) with mixed model analysis.

Results:

Propensity score matching resulted in a comparison of 30 brace patient with 83 HTO patients, and of 28 usual care patients with 71 HTO patients. Pain at 1 year after HTO (VAS 3.8) was lower than after valgus bracing (VAS 5.0) with a mean difference of -1.1 (95% CI -2.2 ; -0.1). Function showed a nonsignificant mean difference of 2.1 [95% CI -3.1 ; 7.3].

Comparing HTO to usual care a difference was seen in pain (-1.7 [95% CI -2.8 ; -0.6]) and function (6.6 [95% CI 0.2 ; 13.1]), in favor of the HTO.

Conclusions:

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Our data suggest that HTO was more effective in pain reduction compared to both non-surgical treatments. Function improved only when HTO was compared to usual care treatment. These small differences question the benefits of surgical treatment over the brace treatment.

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Introduction

To date no randomized controlled trial has compared the HTO with non-surgical treatment in patients with medial knee osteoarthritis (OA) and a varus malalignment. With this study we aimed to fill this gap in the current knowledge. It is known that OA of the knee is a frequent cause of pain and immobility. In the United States, approximately 9% of individuals aged 60 years and older suffer from knee OA (1). An important risk factor for incidence and progression of knee OA is varus malalignment of the knee (2, 3); Patients with a varus alignment of the knee have an increased risk to develop OA of the medial compartment and later on progress to more severe knee OA. Furthermore, the medial compartment is the most commonly affected site in unicompartmental OA (4).

According to the American Academy of Orthopaedic Surgeons (AAOS) guideline, the Osteoarthritis Research Society International (OARSI) guideline and the European League Against Rheumatism (EULAR) recommendation there are various treatment options regarding knee OA, both surgical and non-surgical, available for patients with knee OA. The initial non-surgical treatment consists of patient education, weight reduction, physical therapy, and analgesics. More invasive treatment options are intra-articular injection, or surgery often consisting of a total knee arthroplasty (TKA). Specifically for varus alignment and symptomatic medial knee OA there are some additional options: non-surgical treatment with a lateral wedge, or valgus bracing, and surgical options like a high tibial osteotomy, or a unicompartmental knee arthroplasty (UKA) (5-8). Of the surgical options for the relative younger, active patient the HTO remains the procedure of choice (9, 10). The UKA and the TKA are the preferred options for older patients with end-stage OA.

Randomized controlled trials (RCTs) are considered the gold standard approach for estimating the effects of treatments and interventions on clinical outcome. Random treatment allocation ensures that the effect of treatment will not be confounded by either measured or unmeasured prognostic factors.

Therefore, in an RCT the effect of treatment on outcomes can be estimated by comparing outcomes directly between treated and untreated or differently treated subjects (11). Recently, there is increasing interest in methods based on the propensity score to eliminate the effects of confounding by indication as much as possible when using observational data for the comparison of effects of different treatments. Propensity score methods allow one to mimic equal prognosis, one of the main characteristics of an RCT, in the context of an observational study. The propensity score is defined as the conditional probability of a subject being assigned to the treatment group given the observed covariates (12). As we had the availability to the individual patient data of two previously conducted RCTs with similar inclusion criteria including both non-surgical treatments and HTO treatments, we were able to perform a direct comparison of HTO treatment and non-surgical treatments on clinical outcome by using propensity score matching.

The aim of the present study was to compare the effectiveness of the unloader brace treatment and the HTO treatment regarding pain severity and knee function score in varus aligned medial knee OA patients. Secondary we compared a usual care treatment program and HTO treatment regarding pain severity and knee function score in the same patient group.

Materials and Methods

Study design

We used individual patient data from two previously conducted RCTs. Both RCTs were conducted during the same period in two different hospitals by the same research group. One RCT of 117 patients compared an unloader brace (the OAsys kneebrace, Innovation Sports, Irvine, CA, USA) to a usual care treatment program in a hospital where HTO surgery was not performed (13). The RCT was conducted to study the effect of an unloader brace compared to a usual care program in patients with

unicompartimental knee OA. The unloader brace intended to reduce load of the affected compartment. The usual care program consisted of patient education, physical therapy and analgesics with a 12 months follow-up. In this study both valgus and varus aligned patients with knee OA were included. The primary outcomes were pain (Visual Analogue Scale (VAS)) and knee function (Hospital for Special Surgery Knee-Rating Scale (HSS)) after 12 months follow-up. For our analysis we excluded the valgus aligned patients out of the non-surgical RCT to ensure we only included patients with varus malalignment and medial knee OA, because no valgus OA patients were included in the surgical RCT. This resulted in 22 excluded patients out of the 117 initial patients. The 95 patients with varus alignment were equally distributed between the valgus bracing group (n=48) and the usual care treatment group (n=47).

The second RCT of 92 patients compared lateral closing-wedge with medial opening-wedge osteotomy in patients with medial compartment knee OA (10). The RCT was conducted in a hospital where HTO surgery was a usual treatment option for varus malaligned medial knee OA and studied the achievement and maintenance of adequate operative correction of varus malalignment with 12 months follow-up. In this study 4 surgeons performed the HTO. Secondary pain severity (VAS), walking distance, and knee function (HSS) was studied. After 12 months both groups improved similarly regarding pain reduction and knee function. Therefore, we combined the individual patient data with our propensity score matching for the HTO group and considered them as one group disregarding the used opening or closing wedge procedure.

The inclusion and exclusion criteria for both studies were nearly identical. The following inclusion and exclusion criteria were identical for both studies:

- Patients aged 18 years and older
- Unicompartimental OA was diagnosed when there was pain and tenderness of the joint margins in

combination with osteoarthritic signs according to the Ahlbäck score (Ahlbäck > 0)

- The degree of malalignment was assessed using the hip-knee-ankle angle on a whole leg radiograph in standing position. The hip-knee-ankle angle was defined as the angle between a line (mechanical axis of the femur) from the center of the femur head to the middle of the distance between the tibial spines, and a second line (mechanical axis of the tibia) from the center of the ankle to the center of the tibial spines
- Only one knee was included in the study
- Criteria for exclusion were previous HTO, an insufficient command of the Dutch language, and rheumatoid arthritis

Differences between the studies:

- The unloader brace vs. usual care treatment program study included valgus and varus alignment and therefore lateral compartment knee OA (we excluded those patients before the matching), while the closing-wedge vs. opening-wedge osteotomy study only included patients with varus malalignment and medial compartment knee OA
- The closing-wedge vs. opening-wedge osteotomy study excluded patients when they had a range of motion (ROM) < 100 degrees or a flexion contracture of > 10 degrees, and a history of fracture or open surgery of the lower extremity; we lacked this information in the other RCT

Propensity score matching

First, as stated above we excluded patients with valgus alignment and lateral compartment OA from the brace vs usual care RCT. Thus, we created a dataset of patients with varus alignment and medial compartment knee OA who were treated with a valgus brace, a usual care treatment program, or an HTO.

For both research comparisons we equalized the baseline prognostic factors of the two groups by using propensity score matching. A propensity score was calculated with baseline variables by using logistic regression analysis. The propensity score was based on the following baseline covariates: VAS pain, HSS, age, gender, hip-knee-ankle angle, body-mass-index (BMI), and radiological severity of OA. Because several patients did not complete follow-up we used multiple imputation (MI) to give an estimate of their results. When comparing the HTO to the usual care we missed the VAS pain and HSS of 7 patients (1 HTO and 6 usual care patients). In the comparison of the HTO to the brace we missed the same data of 4 patients (1 HTO and 3 brace patients). In our MI model all known variables were used i.e. treatment, propensity score matching, HKA, VAS (baseline, six, nine and 12 months), HSS (baseline, six, nine and 12 months), BMI, age, gender and radiological OA. The VAS pain and HSS for both analysis was imputated 10 times, when imputing more than 10 times no differences were seen.

One-to-many matching was performed using a variable ratio, parallel and balanced nearest neighbor approach (14). In this approach, we aimed to match each usual care or unloader brace patient with between 1 and 4 HTO patients, based on their propensity scores. In each propensity score matching set a HTO patient could only be used once. So if a HTO patient matched with a usual care patient, this patient could not be reused for another usual care patient. The same one-to-many principle was used when matching the unloader brace patients to HTO patients. During the matching, we applied a caliper width of 0.2 standard deviation (SD) of the propensity score to limit the allowed distance between two matched patients. This method was used to match up to a maximum of four HTO patients to either one usual care patient or one unloader bracing patient.

Outcome assessment and statistical analysis

For the comparison of the effectiveness of the non-operative and operative treatment options we assessed the VAS pain (range 0-10, a higher score indicates greater pain intensity) and HSS score (range

0-100, a higher score indicates better knee function) at 12 months follow-up. In our analysis we adjusted for the baseline scores and calculated the estimated difference with a 95% confidence intervals, and effect size of the treatment.

Differences between the groups at baseline were checked by comparing the means with an independent t-test. The following baseline covariates were taken into account: VAS pain, HSS, age, gender, hip-knee-ankle angle, and radiological severity of OA.

To analyze the clinical effectiveness of the usual care program, and unloader bracing with that of HTO we used a mixed model analysis to account for the correlation in the data due to matching. The dependent variable was either VAS pain or the HSS after 12 months. In this analysis we adjusted for the baseline scores of the VAS pain or the HSS respectively, and for covariates if they influenced the estimate with 10% or more. Finally we estimated the effect size by calculating Cohen's delta.

Results

Valgus bracing vs. HTO

We were able to match 30 valgus brace patients out of 48 with 83 HTO out of 92 patients. Baseline characteristics for the separate groups are shown in table 1. As expected, there were no significant differences between the two groups regarding the baseline characteristics. The inclusion flowchart is shown in figure 1. At 12-months follow-up the estimated mean VAS pain for the valgus brace group was 4.9 while for the HTO group the score was 3.8 which resulted in an estimated mean difference of -1.1 [95% CI -2.2 ; -0.1] with an effect size of 0.5. At 12-months follow-up the estimated mean HSS for the valgus brace group was 76.9 and for the HTO group was 79.4 with an estimated mean difference of 2.1 [95% CI -3.1 ; 7.3]. This is summarized in table 2.

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Usual care treatment vs. HTO

When comparing the usual care treatment to the HTO we were able to match 28 out of 47 usual care treatment patients with 71 out of 92 HTO patients. No differences were found between both groups regarding the baseline characteristics, see table 1. The inclusion flowchart is shown in figure 1. At 12-months follow-up the estimated mean VAS pain for the usual care treatment group was 5.3 while for the HTO group the score was 3.6 which resulted in an estimated mean difference of -1.7 [95% CI -2.8 ; -0.6] with an effect size of 0.6. At 12-months follow-up the estimated mean HSS for the usual care treatment group was 73.1 and for the HTO group was 79.8 with an estimated mean difference of 6.6 [95% CI 0.2 ; 13.1]. This is summarized in table 2.

Discussion

Our data suggest that HTO is more effective in pain reduction after 12 months than either an unloader bracing treatment or a usual care treatment program. HTO also is more effective in knee function improvement than the usual care treatment program. For pain severity the HTO treatment was in favor compared to the brace treatment with an effect size (Cohen's delta) of 0.5 pointing at a clinically relevant difference. Although slightly better after HTO treatment, the improvement in knee function was neither statistically significant nor clinically relevant. The comparison between HTO and non-surgical usual care yielded larger differences both for pain and function outcomes, both statistically significant and pointing at a clinically relevant difference, with an effect size of 0.6. To our knowledge this is the first study to compare a HTO to non-surgical interventions regarding knee OA.

Although an HTO shows better results after 1 year there are several pros and cons regarding HTO. An HTO has good results with respect to pain reduction and long-term results with high survival rates, 70 - 73% at 10-year follow-up (15-17). However, the impact of surgery and complication rates should be

taken into consideration. As shown by several studies (18-22), complications often seen after an HTO are sensory palsy of common peroneal nerve, pain at iliac crest, and hardware removal (18). In the original RCT that was used for this manuscript the most common complications were removal of osteosynthesis material in both groups and Iliac-crest morbidity in the opening wedge group. At one year follow-up two patients, in the opening-wedge group, had a non-union (10). On the other hand there is an ongoing discussion about the effects of valgus bracing. The Cochrane review shows that wearing a brace may lead to a reduction of pain, improved knee function and walking distance, but no improved quality of life (23). However, Brouwer et al. showed better effects in subgroup analysis of varus malalignment medial knee OA (13). Meta-analysis has suggested that there is a small-to-moderate improvement in pain. Possible low compliance, however, remains a factor in the success of treatment with varying rates from 45% to 100% (24). Out of the initial brace group (n=60) in our RCT 25 patients stopped with the bracing treatment. The high dropout rate was due to ineffectiveness, good treatment effect or discomfort (skin irritation and bad fit) (13). Furthermore, long-term benefits and compliance in valgus bracing is poorly reported and therefore mostly unknown (23).

Strengths and limitations

Strength of our study is that we were able to combine the data of two RCT cohorts using propensity score matching and compare a HTO to non-surgical treatment. To date a comparison between HTO and non-surgical treatment (unloader bracing or a usual care treatment program) has not been performed. Propensity scores can be used to compare treatments when RCT data is not (yet) available, or when it is hard to perform an RCT due to ethical or other difficulties. Although an RCT still remains the gold standard it is possible to mimic some of the characteristics of an RCT with propensity score matching (12).

A limitation, of course, is that it is not possible to control for unknown variables with propensity score matching while with an RCT one assumes that unknown variables are distributed among the groups equally. This leads to the issue of possible confounding by indication for surgical vs. non-surgical. While study patients in the RCTs used for the propensity score matching all were included according to the same inclusion criteria, it still is possible that we have missed confounding factors like for instance general health factors, and treatment preference of patient and clinician.

Another potential limitation is that the surgical RCT was a single center study, and the non-surgical RCT was a multicenter study. The large majority of the patients were recruited in different hospitals. This might have resulted in slightly different populations. However, in the hospital where the majority of the patients for the brace vs. usual care RCT were included no HTO surgery was performed, therefore, we believe that selection bias was limited. Although, the assessor in both RCTs was the same researcher and was blinded to the patient allocation, patients were not blinded to their treatment. They were, however, not aware of the present comparison. Finally, we have to emphasize that the results in this study only apply to the group of OA patients with medial knee OA and varus alignment.

Future research

Previous HTO RCT studies have shown good results in terms of pain reduction and improvement of function with good long-term follow-up (22, 25, 26). However, patient selection, complication rates and rehabilitation time leaves room for debate regarding the treatment and/or optimal timing of surgery. Furthermore, long-term follow-up in valgus bracing regarding compliance and effect is still unknown, and although we found an indication for a possible clinically relevant effect on pain of HTO above that of bracing, we did not find this for function. A possible explanation for the difference in pain between could be the surgical effect regarding pain. Several studies have shown the similar effect of sham surgery and arthroscopy regarding pain (27, 28). Because of the lack of studies comparing a HTO with

non-surgical treatments we believe our results partly fill the gap in the current knowledge regarding the work-up in varus malaligned medial knee OA. However, the only small to moderate effects of HTO compared to brace treatment strongly call for a direct comparison between these treatments in a formal RCT design.

In conclusion the results show that an HTO is more effective in pain reduction than both an unloader brace and a usual care treatment program at 12 months follow-up. However, knee function improved only when HTO was compared to usual care treatment. Since the difference between HTO and brace treatment was small, these findings question the benefits of a surgical treatment over the brace treatment. However, the mid-term follow-up in brace treatment is unknown in terms of treatment survival and clinical outcome.

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Conflict of interest

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Author contributions

All authors made a substantial contribution to the conception and design of the submitted manuscript. They also contributed to the drafting and revising of the manuscript and gave their final approval of the submitted version.

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Table 1. Baseline characteristics of the treatment groups

	Valgus unloader brace (n=30)	**HTO (n=83)**
Baseline characteristics		
Women, n (%)	10 (33.3)	32 (38.6)
Age, years	51.5 (± 9.6)	51.4 (± 7.4)
BMI, kg/m^2	28.8 (±4.7)	28.3 (± 5.1)
HKA, degrees	6.9 (± 3.2)	6.2 (± 2.8)
VAS (0-10)	6.4 (± 2.1)	6.2 (± 1.7)
HSS (0-100)	69.5 (± 10.5)	71.1 (± 9.7)
Ahlbäck score	1.1 (± 0.3)	1.1 (± 0.4)

	Usual Care Treatment (n=28)	**HTO (n=71)**
Baseline characteristics		
Women, n (%)	13 (46.4)	26 (36.6)
Age, years	53.6 (± 11.2)	51.7 (± 6.8)
BMI, kg/m^2	29.4 (± 5.5)	28.6 (± 5.2)
HKA, degrees	7.2 (± 3.9)	6.4 (± 2.9)
VAS (0-10)	5.7 (± 1.9)	5.9 (± 1.8)
HSS (0-100)	72.8 (± 9.9)	71.9 (± 9.7)
Ahlbäck score	1.18 (± 0.4)	1.13 (± 0.4)

Data is presented as means with standard deviation between parentheses unless reported otherwise

VAS: A higher score indicates greater pain intensity

HSS: A higher score indicates better knee function

Table 2. 12-months follow-up

	Unloader brace (n=30) Absolute mean	**HTO (n=83) Absolute mean**	**Unloader brace (n=30) Estimated mean**	**HTO (n=83) Estimated mean**	**Estimated mean difference (p-value) & [95% CI]**
VAS (0-10)	5.0 (±2.7)	3.8 (±2.6)	4.9	3.8	-1.1 (p=0.04) [-2.2 ; -0.1]
HSS* (0-100)	76.9 (±10.5)	79.4 (±12.8)	76.7	78.8	2.1 (p=0.43) [-3.1 ; 7.3]
	Usual Care (n=28) Absolute mean	**HTO (n=71) Absolute mean**	**Usual Care (n=28) Estimated mean**	**HTO (n=71) Estimated mean**	**Estimated mean difference (p-value) & [95% CI]**
VAS (0-10)	5.2 (±2.5)	3.6 (±2.6)	5.3	3.6	-1.7 (p=0.002) [-2.8 ; -0.6]
HSS (0-100)	73.4 (±14.8)	79.6 (±13.3)	73.1	79.8	6.6 (p=0.043) [0.2 ; 13.1]

Data is presented as means with standard deviation between parentheses unless reported otherwise

VAS: A higher score indicates greater pain intensity

HSS: A higher score indicates better knee function

*: adjusted for gender in mixed model analysis

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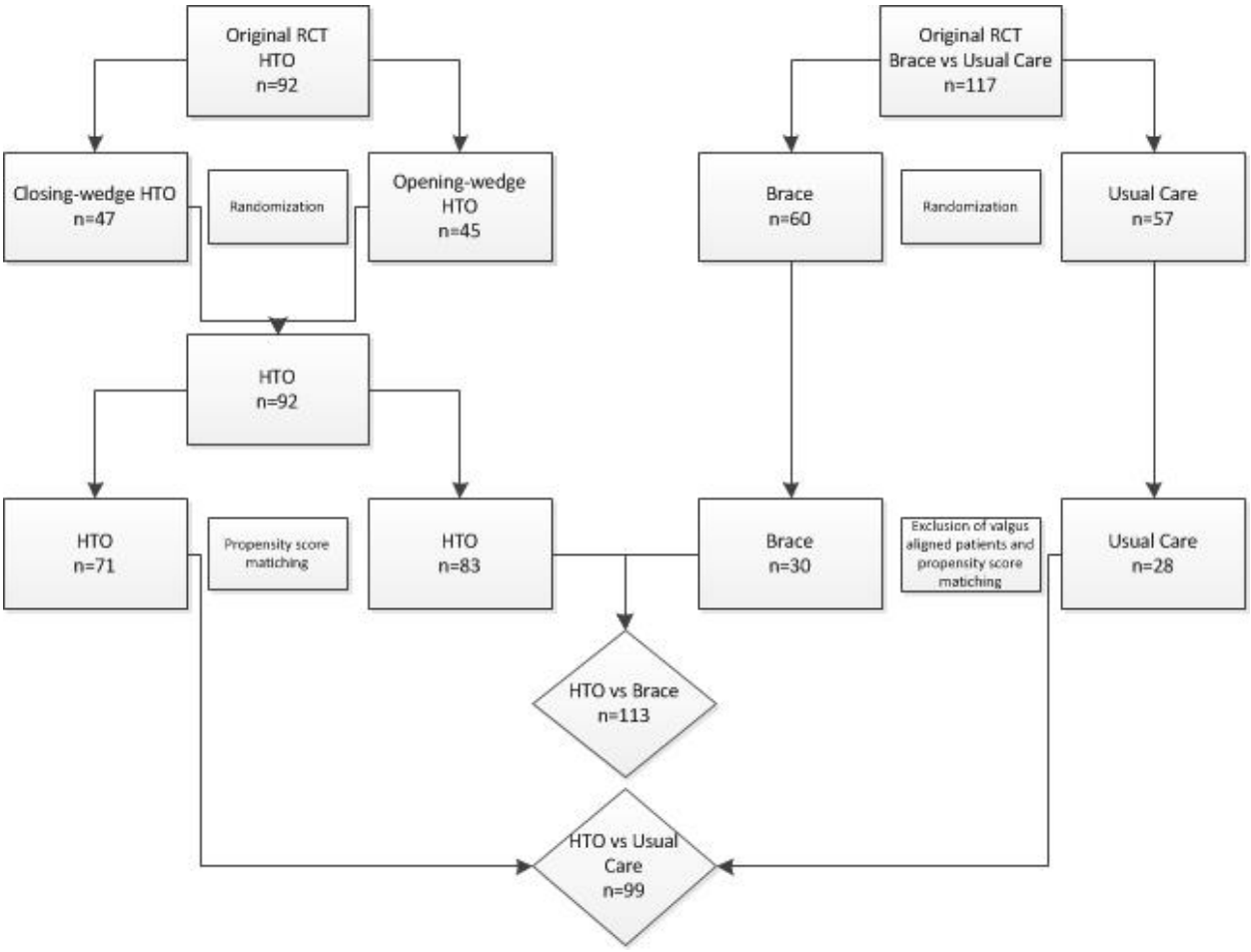
Figure 1. Flowchart: propensity score one-to-many matching



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