Blinded interpretation for the primary and secondary outcomes for the primary endpoint for the NEPNEP trial

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Blinded interpretation of the primary and secondary outcomes for the primary endpoint for the trial

The NEPNEP trial – a randomized controlled trial for chronic pain after primary total knee arthroplasty

As described in the statistical analysis plan[1] that was published before data collection was finished and before data analysis was initiated, a blinded interpretation of the results was made. The treatment groups were coded as "group 1" and "group 2" and delivered to the blinded statistician in the data collection form. The statistician conducted the intention-to-treat analysis for the primary and secondary outcomes for the primary endpoint (from baseline to 12-months follow-up). The results were presented to the first author, who was responsible for presenting the results to the study group. Thereafter, the results underwent blinded interpretation by the study group (which are the persons signing this document). Before the treatment allocation code was broken, the study group agreed on a final version of the interpretation.

This document contains the blinded interpretation of the results in two versions. One version in which "group 1" was the group receiving the 12-week supervised neuromuscular exercises and pain neuroscience education (PNE), and one version in which "group 1" was the group receiving PNE alone.

To keep the blinding of group allocation intact, adverse events were not analyzed in preparation for blinded interpretation. Neither were group numbers (n) presented in the results. Once the blinding has been broken, all pre-defined analysis will be conducted, including a per protocol analysis which will be part of the main publication. These results will be taken into consideration in the overall interpretation of the study results.

Intention to treat analysis:

Between-group difference for the main outcome:

There was no significant difference between group 1 and 2 for the primary outcome $KOOS_4$ (Knee injury and Osteoarthritis Outcome Score) which consist of the average scores of the four KOOS subscales Pain, Symptoms, activity of daily living and knee-related quality of life. Group 1 experienced a mean improvement of 7.5 (95% CI 3.0 to 11.9) and group 2 had a mean improvement of 8.7 (95% CI 4.7 to 12.6) from baseline to 12-months follow-up. The between-group difference for $KOOS_4$ was 1.3 (95% CI -7.6 to 4.9) (supplementary table 1). The responder analysis showed that 36% of the patients in group 1 and 33% of the patients in group 2 experienced clinically important improvements from baseline to 12-months follow-up. There was no difference in proportion of responders between the groups.

[1] Statistical analysis plan can be found here: https://vbn.aau.dk/da/publications/statistical-analysis-plan-for-the-nepnep-trial-a-randomized-contr

Between-group differences for the secondary outcomes:

There were no significant between-group differences in change in the five KOOS subscales of pain, symptoms, activity of daily living, sport/recreation and knee-related quality of life, global perceived effect, time to complete the 40meter fast paced walk test, time to complete the stair climb test, or numbers of repetitions in the 30sec chair stand test (supplementary table 1). Neither was there any significant between-group differences for usage of pain medication.

Within-group changes:

Both group 1 and group 2 experienced significant improvements in all primary and secondary outcomes except for usage of pain medication in which neither group 1 or 2 showed an improvement, for the KOOS subscale sport/recreation in which group 1 showed no improvement and for the 40meter fast-paced walk test in which group 2 showed no improvement.

Interpretation 1: "Group 1 received neuromuscular exercises and pain neuroscience education"

This is the first randomized controlled trial of patients with chronic pain after total knee arthroplasty (pain for at least 6 months and at least 1-year post-operative) evaluating treatment effect.

Our results demonstrate no between-group difference for the primary outcome $KOOS_4$ for patients with chronic pain after total knee arthroplasty receiving neuromuscular exercises and pain neuroscience education (PNE) compared to patients receiving PNE alone. Likewise, no between-groups differences were reported for the secondary outcomes of the KOOS subscales pain, symptoms, activity of daily living, sport/recreation, knee-related quality of life, the physical performance tests of 40meter fast-paced walk test, stair climb test and the 30sec chair stand test and the risk of pain medication usage.

Both groups improved in most outcomes from baseline to 12 months follow-up. The improvements for the main outcome $KOOS_4$ did not reach the pre-specified minimally clinically important difference (MCID) of 10 points. Similarly, the KOOS subscales improvements did not reach the MCID of 10 points, except for knee-related quality of life which improved 10 points in the group receiving neuromuscular exercises and PNE.

The study provides evidence that both treatment options provide improvements, though below the pre-specified MCID level. Importantly, 36% of patient receiving neuromuscular exercises and PNE and 33% of patients receiving PNE alone experienced clinically relevant improvements from baseline to 12-months follow-up. This observation highlights that about 1/3 of patients with chronic pain after TKA can experience clinically important improvements, despite their longstanding and treatment-resistant condition.

Overall, the results did not support the hypothesis stating that neuromuscular exercise and PNE would lead to greater pain relief and improved physical performance than PNE alone.

Interpretation 2: "Group 1 received the pain neuroscience education alone"

This is the first randomized controlled trial of patients with chronic pain after total knee arthroplasty (pain for at least 6 months and at least 1-year post-operative) evaluating treatment effect.

Our results demonstrate no between-group difference for the primary outcome $KOOS_4$ for patients with chronic pain after total knee arthroplasty receiving neuromuscular exercises and pain neuroscience education (PNE) compared to patients receiving PNE alone. Likewise, no between-groups differences were reported for the secondary outcomes of the KOOS subscales pain, symptoms, activity of daily living, sport/recreation, knee-related quality of life, the physical performance tests of 40meter fast-paced walk test, stair climb test and the 30sec chair stand test and the risk of pain medication usage.

Both groups improved in most outcomes from baseline to 12 months follow-up. The improvements for the main outcome $KOOS_4$ did not reach the pre-specified minimally clinically important difference (MCID) of 10 points. Similarly, the KOOS subscales improvements did not reach the MCID of 10 points, except for knee-related quality of life which improved 10 points in the group receiving PNE alone.

The study provides evidence that both treatment options provide improvements, though below the pre-specified MCID level. Importantly, 36% of patient receiving neuromuscular exercises and PNE and 33% of patients receiving PNE alone experienced clinically relevant improvements from baseline to 12-months follow-up. This observation highlights that about 1/3 of patients with chronic pain after TKA can experience clinically important improvements, despite their longstanding and treatment-resting condition.

Overall, the results did not support the hypothesis stating that neuromuscular exercise and PNE would lead to greater pain relief and improved physical performance than PNE alone.

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Supplementary:

Table 1: Overview of the blinded results for the primary and secondary outcomes from baseline to 12-months follow-up.

Outcome (number of data points$_{group1}$, number of data points$_{group2}$)	**Improvement in group 1 (95% CI)**	**Improvement in group 2 (95% CI)**	**Between-group difference (crude) (95% CI)**	**Between-group difference (adjusted) (95% CI)**
Primary outcome				
$KOOS_4$ (xx, xx)	7.46 (3.04 to 11.89)	8.65 (4.67 to 12.63)	-1.19 (-7.14 to 4.76)	-1.33 (-7.59 to 4.92)
Secondary outcomes				
KOOS Pain (xx, xx)	6.41 (1.51 to 11.30)	9.85 (5.82 to 13.87)	-3.44 (-9.77 to 2.90)	-4.02 (-10.85 to 2.82)
KOOS Symptoms (xx, xx)	6.96 (0.04 to 13.87)	8.23 (1.86 to 14.59)	-1.27 (-10.67 to 8.13)	-1.62 (-11.50 to 8.26)
KOOS ADL (xx, xx)	4.49 (0.19 to 8.80)	7.66 (1.83 to 13.49)	-3.16 (-10.41 to 4.08)	-3.66 (-10.79 to 3.47)
KOOS Sport/Recreation (xx, xx)	5.06 (-0.08 to 10.19)	9.41 (3.05 to 15.77)	-4.35 (-12.52 to 3.83)	-5.40 (-13.25 to 2.46)
KOOS Quality of life (xx, xx)	10.60 (4.11 to 17.09)	9.79 (3.64 to 15.94)	0.81 (-8.13 to 9.75)	1.81 (-6.86 to 10.48)
Global Perceived effect (xx, xx)	2.82 (2.24 to 3.39)	2.80 (2.27 to 3.33)	0.02 (-0.77 to 0.80)	0.02 (-0.82 to 0.86)
Time to walk 40 meter (xx, xx)	-3.11 (-5.66 to -0.56)	-1.68 (-4.65 to 1.28)	-1.43 (-5.34 to 2.48)	-0.97 (-5.19 to 3.25)
Stair climbs (sec) (xx, xx)	-2.53 (-4.73 to -0.33)	-1.99 (-3.54 to -0.43)	-0.55 (-3.24 to 2.15)	-0.42 (-3.26 to 2.43)
30sec. chair stand (reps.) (xx, xx)	0.93 (0.22 to 1.63)	1.88 (0.96 to 2.79)	-0.95 (-2.11 to 0.21)	-1.05 (-2.26 to 0.16)

KOOS: Knee injury and Osteoarthritis Outcome Score. ADL: Activities of daily living. Number of data points are not displayed to ensure the blinded interpretation. Crude: Estimates are from a linear mixed model adjusting for patient, follow-up, treatment arm and interaction between follow-up and treatment arm. Adjusted: Estimates are from a linear mixed model adjusting for patient, follow-up, age, sex, body-mass index, treatment arm and interaction between follow-up and treatment arm.