Conclusion: The dedicated KJD device provides user-friendly equipment for clinicians and patients, as indicated by the shorter intervention duration and patient questionnaire outcomes, and contributes to further implementation of KJD as treatment for end-stage knee OA.

References:

[1] MP Jansen *et al*, PLOS ONE 2020

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FRI0408

KNEE JOINT DISTRACTION AS TREATMENT FOR OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Knee osteoarthritis (OA) is a common cause of invalidity and is often treated with a total knee arthroplasty (TKA). While TKA is cost-effective, reduces pain and improves function, it brings a greater risk of a future revision surgery when performed in younger patients. Knee joint distraction (KJD) is a joint-preserving OA treatment that may postpone TKA and possibly prevent a revision. In the past years, multiple studies have investigated this surgical treatment.

Objectives: To evaluate short- and long-term clinical benefit and tissue structure changes after KJD treatment for knee OA.

Methods: MEDLINE, EMBASE and Web of Science were searched for eligible clinical studies evaluating a change in at least one of: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Score of pain (VAS-pain), Knee injury and Osteoarthritis Outcome Score (KOOS), EuroQol-5D (EQ5D), radiographic joint space width (JSW) or MRI cartilage thickness after KJD. The primary clinical and structural outcome parameters were the WOMAC and minimum JSW, respectively. Random effects models were applied on all outcome parameters and outcomes were compared with control groups found in the included studies. For continuous data the mean difference (MD) and 95% confidence interval (95%CI) were calculated and for dichotomous data the risk difference and 95%CI, following the Cochrane handbook.

Results: In total 11 articles reporting on 7 different KJD cohorts with in total 127 patients and 5 control groups at multiple follow-up moments were included, with 2 of the studies being randomized controlled trials (RCTs). The WOMAC (figure 1) was compared to pre-treatment in 3 cohorts after 1 year (patients n=62) and 2 years (n=59) and in 1 cohort after 5 years (n=20) and 9 years (n=8), showing a significant increase at all time points (all p<0.001). The VAS-pain showed similar results at the same 4 time points, as did the KOOS and EQ5D, which were evaluated only after 1 (n=42) and 2 (n=39) years.

The minimum (figure 2) and mean JSW are reported in 3 cohorts after 1 (n=59) and 2 (n=59) years and in 1 cohort after 5 (n=20) and 7 (n=8) years. Both JSW measures were statistically significantly increased after 1 and 2 years, but after 5 and 7 years the JSW increase was no longer statistically significant. Similarly, the MRI cartilage thickness showed an increase at 1 and 2 years, but not at 5 years (all n=20).

Complications were reported in 5 studies with 87 patients, with 57 patients developing one or more pin tract skin infections, giving a risk of pin tract infections of 63% (95%CI 45-81), the majority of which could be treated with oral antibiotics. Only a small amount of other complications occurred and were all treated successfully.

Overall, clinical and structural outcomes were comparable with control groups, including high tibial osteotomy and TKA as compared after 1 and 2 years in the two RCTs. Apart from pin tract infections, complications were not different in severity and number between control groups and KJD.

Conclusion: KJD causes clear benefit in clinical and structural parameters over time, short- and long-term. Although the total number of patients is limited, effect sizes are large. Longer follow-up with more patients is necessary and could improve patient selection for this intensive treatment, while preventing pin tract infections could lighten the patients' treatment burden. Irrespectively, KJD provides an additional option in joint-preserving treatments for OA and a viable alternative to joint replacement, especially in younger patients.

Figure:

Figure 1: Change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score 1, 2, 5 and 9 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. SD: standard deviation; CI: confidence interval.

Figure 2: Change in minimum joint space width (JSW) 1, 2, 5 and 7 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. SD: standard deviation; CI: confidence interval.

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PREVALENCE AND FACTORS ASSOCIATED WITH CHRONIC PAIN WITH NEUROPATHIC CHARACTERISTICS IN PATIENTS WITH KNEE OSTEOARTHRITIS IN CAMEROON, SUB-SAHARAN AFRICA

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Background: Recent studies suggest that pain in osteoarthritis (OA) is not only nociceptive, but also has neuropathic characteristics (1). To our knowledge, no study has been carried out in sub-Saharan Africa to assess the neuropathic pain associated with knee OA.

Objectives: To determine the prevalence of chronic pain with neuropathic characteristics and associated factors in patients with knee OA in Cameroon.

Methods: We performed a cross-sectional study at the Douala General Hospital from December 2018 to April 2019. Patients over the age of 21 with a diagnosis of knee OA (ARA, 1986; Kellgren–Lawrence radiographic grading ≥ 2) were included. The intensity of the pain was measured using the visual analog scale. Neuropathic pain was detected using the DN4 questionnaire with a cut-off at DN4 ≥ 4 (2) and functional impairment assessed using the Lequesne algofunctional index. Logistic regression analysis was used to assess the association between patients' characteristics and DN4. The $p < 0.05$ was considered significant.

Results: We included 151 patients (120 women) with knee OA, mean age at 59.8 ± 12.8 years (31 to 86) years, with a mean duration of knee OA at 38 ± 44.9 months and a mean BMI at $30.4 \pm 6.2 \text{ kg/m}^2$.

The mean DN4 score was 2.5 ± 2 . It was higher in women compared to men (2.7 ± 2 vs. 1.9 ± 1.7 ; $p = 0.04$). Tingling (58.9%) was the most frequently encountered item in the DN4 questionnaire (Table 1). A DN4 ≥ 4 was found in 41 patients (27.1%). Patients with neuropathic pain (DN4 ≥ 4) were older (63.7 ± 10.6 years vs. 58.4 ± 13.2 ; $p = 0.02$) and had higher VAS pain (6.17 ± 1.6 vs. 5.02 ± 1.5 ; $p < 0.01$) than patients without neuropathic pain (DN4 < 4). In multivariate analysis, only the intensity of pain $\geq 70 \text{ mm}$ (OR = 2.1, 95%CI: 1.1–5.5; $p = 0.02$) and a Lequesne index ≥ 11 (OR = 2.4, 95% CI: 1.1–6.7; $p = 0.04$) were associated with neuropathic pain. Patient's age at diagnosis, sex, occupation, monthly income, radiological characteristics, BMI, joint effusion, duration of illness, and the existence of comorbidities such as low back pain, diabetes, or hypertension were not associated with the diagnosis of neuropathic pain ($p < 0.05$).

Table 1. Frequency of items in the DN4 questionnaire

DN4 items	Frequency, n (%)
Interview of the patient	
Question 1	Burning 58 (38.4)
	Painful cold 8 (5.3)
	Electric shocks 50 (33.1)
Question 2	Tingling 62 (41)
	Pins and needles 89 (58.9)
	Numbness 68 (45)
	Itching 14 (9.2)
Examination of the patient	
Question 3	Hypoesthesia to touch 16 (10.6)
	Hypoesthesia to pinprick 8 (5.3)
Question 4	Brushing 22 (14.5)

Table 2. Univariate and multivariate logistic regression analysis of factors associated with neuropathic pain

Variables	CateLgory	Unadjusted OR	95% CI	p	Adjusted OR	95% CI	P
Age, year	<40	0.2	0-2.2	0.37			
	40-65	1.4	0.1-2.9	0.43			
	>65	0.5	0.2-1.1	0.14			
Sex	Female	2.2	0.7-6.2	0.18			
	Male	1					
Occupation	Student	1.3	0.1-15.3	1			
	Employed	3.1	1.3-6.9	0.008	1.4	0.3-4.4	0.54
	Unemployed	2.6	1.2-5.4	0.01	0.9	0-2.8	0.87
	Retired	1.1	0.4-2.9	1			
Education	Primary	0.59	0.2-1.3	0.27			
	Secondary	1.5	0.7-3.1	0.34			
	University	0.1	0-0.5	0.02	0.2	0-9	0.05
	Illiterate	0.53	0-1.2	0.56			
BMI	Normal	1.6	0.6-4.1	0.39			
	Overweight	1.8	0.8-4.2	0.2			
	Obesity	0.7	0.3-1.4	0.49			
Comorbidities	Hypertension	0.6	0.3-1.4	0.38			
	Diabetes	0.4	0.1-1.2	0.2			
	Low back pain	0.5	0.3-1	0.1			
	Joint effusion	1.1	0.5-2.9	0.96			
Pain, VAS	Mild pain	3.1	0.8-11	0.1			
	Moderate pain	1.6	0.7-3.3	0.25			
	Severe pain	0.2	0.1-0.6	<0.01	0.4	0.2-0.9	0.03
Disability	Moderate handicap	0.5	0.2-1.4	0.32			
	Severe handicap	1.3	0.7-2.9	0.48			
	Very severe handicap	0.3	0.1-0.6	<0.01	0.3	0.1-0.7	0.04
Kellgren – Lawrence	Grade 2	1.7	0.8-3.5	0.19			
radiographic	Grade 3	0.64	0.3-1.3	0.32			
grading	Grade 4	0.6	0.2-1.9	0.35			

Conclusion: Neuropathic pain exists during knee OA. We found it in 27.1% of patients followed in a hospital in Cameroon. It is associated with the severity of pain and functional disability.

References:

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- [2] Bouhassira D, et al. 2005.

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FRI0411

SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS IN HEALTHY MALE JAPANESE SUBJECTS OF THE ADAMTS-5 INHIBITOR S201086/GLPG1972, A POTENTIAL NEW TREATMENT IN OA

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Background: The disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is a key enzyme in OA (Verma P, et al. J Cell Biochem 2011;112:3507-14). In preclinical models of OA, S201086, a potent and selective ADAMTS-5 inhibitor, protects from cartilage degradation (Clement-Lacroix, et al. Osteoarthritis Cartilage 2017;25:S58). Therefore, S201086 is co-developed by Servier and Galapagos (GLPG1972) as a potential new treatment in OA.

Objectives: This phase I study was to assess and compare the safety, tolerability, pharmacokinetics and pharmacodynamics of S201086 in healthy male Japanese and Caucasian subjects.

Methods: Six ascending single doses of S201086 (50 to 1500 mg) were administered orally as tablets in fasting conditions in 6 groups of 8 Japanese subjects (aged 20-45 years) and 3 ascending multiple doses (300, 600 or 1050 mg/day for 14 days) were administered orally as tablets in fed conditions in 3 groups of 8 Japanese subjects. Additionally, 2 cohorts of 8 Caucasian subjects received either a single oral dose of 300 mg or repeated oral dose of 300 mg once daily for 14 days. In each group, 6 subjects received S201086 and 2 placebo. Plasma was collected at several time points for the quantification of S201086 by LC-MS/MS. Plasma pharmacokinetic parameters were calculated via non-compartmental analysis using Phoenix® WinNonlin® software. Pharmacodynamics was assessed by measurement of the aggrecan ARGS neopeptide levels in serum by ELISA.

Results: No serious adverse drug reactions were observed after administration of single and multiple ascending doses of S201086 in either Japanese or Caucasian subjects. Most adverse events were of mild to moderate intensity and were resolved by the end of the study. Following single administration to Japanese subjects, C_{max} and AUC increased proportionally with doses from 50 to 600 mg and slightly less than dose-proportionally from 600 to 1500 mg, consistent with what was previously observed in the first in-human study in healthy Caucasian subjects (van der Aar E, et al. Osteoarthritis Cartilage 2018;26:S310). In Japanese subjects, after 14-days administration, a limited 1.2- to 1.4-fold accumulation was observed on both C_{max} and AUC at Day14 as compared to Day1, and the steady-state exposure increased dose-proportionally within the 300-1050 mg dose range. Taking the inter-subject variability into account, no difference was observed in C_{max} and AUC between Caucasian and Japanese subjects after single administrations of 300 mg and repeated administrations of 300 mg once daily for 14 days. The serum ARGS neopeptide levels decreased between baseline and last day of treatment for S201086-treated subjects but not for subjects receiving placebo. This decrease was similar for the 3 tested doses in Japanese subjects and was significant as compared to the placebo-treated subjects.

Table. Comparison of ARGS concentration relative change from baseline to last day of treatment according to dose in Japanese participants

		S 201086 300mg (N = 6)	S 201086 600mg (N = 6)	S 201086 1050mg (N = 6)	Placebo (N = 6)
Descriptive Statistics (D14 pre-dose – Baseline) / Baseline	n	6	6	4	6
	Mean $\pm$ SD	-42.67 $\pm$ 8.81	-53.70 $\pm$ 6.50	-54.11 $\pm$ 5.20	13.35 $\pm$ 16.53
Statistical analysis	E (SE)	56.01 (6.156)	67.04 (6.156)	67.45 (6.883)	
	95% CI	43.08; 68.95	54.11; 79.97	52.99; 81.91	
	p-value	< 0.0001	< 0.0001	< 0.0001	

Conclusion: S201086 was shown to be safe and well-tolerated in Japanese and Caucasian healthy male subjects with a suitable PK profile and a significant decrease of the ARGS neopeptide, indicating target engagement. A global Phase 2 study to evaluate the efficacy of S201086 in patients with knee OA is ongoing (NCT03595618).