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Assessment of popliteal neurovascular safety during all-inside suturing of the posterior horn of the lateral meniscus using Upright MRIs of the knee joint

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Abbreviations: BMI, Body Mass Index; ext, extension; flex, 90°-flexion; MRI, magnetic resonance imaging; pNVB, popliteal neurovascular bundle; PCL, posterior cruciate ligament; PHLM, posterior horn of the lateral meniscus.

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1. Introduction

With advanced understanding of meniscal function and accelerated degenerative changes after meniscal tissue resection, treatment strategies of meniscal tears have evolved considerably from removal of the meniscus to preservation procedures, when possible [1–4]. Common meniscal repair techniques include inside-out, outside-in and the arthroscopic all-inside suturing methods, of which the latter has increased in popularity, as these systems state a faster and less invasive method with reduced morbidity [1,5]. Also in case of meniscus allograft transplantation, all-inside repair systems serve as a favourable alternative during repair of the posterior third [6]. All-inside repair techniques have proven to represent a safe surgical procedure, yet, injury of the popliteal neurovascular bundle (pNVB) is a rare but severe complication, which can eventually lead to grave sequelae including fistulas, pseudoaneurysms, need for secondary interventions and even irreversible ischemia with amputation of the limb [7–9]. Here, due to its close anatomical proximity to the pNVB, all-inside suturing of the posterior horn of the lateral meniscus (PHLM) demands for particular caution [10]. In order to improve predictability and minimize the risk of neurovascular complications, previous studies analysed the localization of the neurovascular bundle and its relation to the lateral meniscus depending on demographic aspects, positioning of the knee joint or selection of arthroscopic portal [11–18]. These studies suggested a figure-of-four position, as regularly performed during surgery, to be favourable, yet, with regards to demographics and portal selection, results remained contradictory and there is only limited data on meniscal tear localization [11–17,19]. Furthermore, knowledge on the impact of arthroscopic irrigation fluid in the knee joint on the proximity of the PHLM to the pNVB is lacking. In an attempt to realistically mimic intraoperative conditions, the purpose of this retrospective study (case series, Level of Evidence: IV) was to analyse Positional Upright MRIs of the knee joint and herewith (1) compare the distance of the PHLM to the pNVB in extended and 90°-flexed position, (2) analyse its correlation to demographic data and the impact of intraarticular fluid with possible distension of the capsule and (3) evaluate arthroscopic portal safety depending on suture localization in both knee positions.

We hypothesized that the figure-of-four position and presence of intraarticular fluid might reduce the risk of neurovascular complications and that demographic characteristics might impact anatomical proximity. We also hypothesized that portal safety depends on meniscal suture/tear localization.

2. Materials and methods

2.1. Study design and study group

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and meets the ethical standards of this journal. Verbal informed consent was obtained before commencement and IRB approval for the study was obtained from the review board of the hospital. Sixty-one MRIs of 56 patients (male: $n = 33$, age 54.6 ± 14.7 years; female: $n = 23$, age 48.4 ± 16.6 years), who underwent upright MRI of the knee joint at one single MRI institute between November 2014 and February 2020, were examined in this retrospective study. Inclusion criteria were patients aged 18 years or older and upright MRI performed in both extension and 90° flexion of the knee joint during the same MRI investigation. Exclusion criteria were the following: prior surgery, injuries of the anterior or the posterior cruciate ligaments, acquired knee deformity (prior fractures of the tibial plateau or the distal femur) or incidental findings influencing the position of the NVB (baker cysts, arteriovenous malformations, etc.). Five patients of the cohort underwent MRI of both knee joints either simultaneously or at different time points.

Twenty MRI investigations of 19 patients were excluded from the study; 12 had previously undergone anterior cruciate ligament reconstruction surgery, 3 were younger than 18 years, 2 had previously suffered from tibial plateau fracture and one patient had a large baker cyst. In 2 cases, MRI examination was performed in 60° instead of 90° flexion. Information on patients' demographic characteristics is presented in [Table 1](#).

2.2. Magnetic resonance imaging and analysis

MRI scans were performed using the FONAR Upright™ Positional™ MRI scanner (FONAR Corp., Melville, NY, USA), a 0.6 Tesla open magnet. Patients were placed standing on the positional MRI bed at a reclined angle of 30° to adopt a representative weight-bearing position that could be maintained during image acquisition. MRI scans were performed with knee at full extension and flexion of 90°. For extended position the following sequences were applied: coronal and sagittal T1-weighted (T1W) SE-sequences, axial and coronal T2-weighted (T2W) GE-sequences, sagittal PD-weighted (PDW) sequences and sagittal STIR-sequences. For 90°-flexion position the following sequences were applied: coronal T1W SE-sequences, sagittal T2W FSE-sequences and axial T2W GE-sequence. The images were analysed digitally with a picture archiving and viewing software (JiveX, Visus, Bochum, Germany). Radiological assessments were performed by two experienced clinicians. Measurements were performed following the methods described by Gilat et al. [13]. Axial T2W images of both extended and 90° flexed knee joint of the most superior axial slice through the lateral meniscus were selected after exact confirmation with concurrent localization on sagittal and coronal views. First, the pNVB was identified and encircled. Distance **D** was defined as the shortest distance between the posterior border of the posterior horn of the lateral meniscus and the most anterior point

Table 1
Demographic data and baseline characteristics of the study population.

Demographic data/Baseline characteristics	
Patients/knees examined (n)	56/61
Age (years, mean \pm SD, range)	50.9 \pm 15.8 (19–75)
Gender (male/female, n)	33/23 (patients); 37/24 (knees)
Side affected (right/left, n)	32/29
Height (cm, mean \pm SD, range)	176.3 \pm 9.0 (159–194)
Weight (kg, mean \pm SD, range)	76.0 \pm 13.5 (49–107)
BMI (kg/m ² , mean \pm SD, range)	24.3 \pm 3.2 (18.4–31.0)

of the pNVB in millimetres (Figure 1 a and b). For portal safety analysis for all-inside suturing of the PHLM, altogether 4 arthroscopy portal entry points were simulated: one each at the medial and lateral edges of the patellar tendon and 1 cm further medial and 1 cm further lateral, respectively (1 cm-medial, medial, lateral and 1 cm-lateral portal, Figure 2 a). Trajectory lines were then drawn from each portal to the PHLM at increasing distance from the posterior cruciate ligament (0 mm, 3 mm, 6 mm, 9 mm and 12 mm). Distance *d* was measured from each of these lines to the pNVB (Figure 2 b-e). Numbers of transections were counted, and average values of *d* were compared between the 4 portals at increasing distances from the posterior cruciate ligament. Joint effusion was assessed semi-quantitatively on axial and sagittal MRI scans according to the maximal potential distension of the synovial cavity and distension of $\geq 33\%$ was rated as effusion [20].

2.3. Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 software (GraphPad software, San Diego, USA). Continuous and categorical variables were expressed as mean \pm standard deviation (range) and n, respectively. Distances were compared using both paired or unpaired Student's t-test depending on the respective subgroup analysis. Correlations between distance measurement and demographic characteristics were analysed using Pearson coefficient *r*. For comparison of distance *d* from the all-inside device trajectory lines to the pNVB among all different portals one-way ANOVA test was applied. *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Evaluation of distance *D* according to knee positioning and demographic aspects

Average distance *D* between the NVB and the PHLM was significantly longer in 90°-flexion position with 17.3 \pm 6.0 mm (8.2–34.5) than in extended knees with 11.3 \pm 4.2 mm (5.0–20.9) in pairwise comparison ($p < 0.0001$, Figure 3). In 59 of 61 (96.7%) analysed MRIs distance *D* was longer in 90°-flexion compared to extended position. Knee joints of male patients showed significantly longer distances *D* than those of female patients in both extended and 90°-flexed position (ext: male 12.2 \pm 3.9 mm (6.4–20.9) vs. female 9.8 \pm 4.4 mm (5.0–19.5), $p = 0.028$ and 90° flex: male 18.9 \pm 6.6 mm (8.6–34.5) vs. female 14.9 \pm 4.1 mm (8.2–22.5), $p = 0.011$, respectively). Correlation analysis of distance *D* and patients' BMI revealed that shorter distances were significantly associated with lower BMI values in both extension and flexion (ext: $r = 0.53$, $p < 0.0001$ and 90° flex: $r = 0.48$, $p = 0.0003$). Also, shorter distance *D* correlated significantly with lower body weight in both extended and flexed knee position (ext: $r = 0.49$, $p = 0.0002$ and 90° flex: $r = 0.48$, $p = 0.0003$). With regard to patients' age, shorter distances were associated with younger age in extended position, yet in 90°-flexion no significant correlation was found (ext: $r = 0.44$, $p = 0.0004$ and 90° flex: $r = 0.22$, $p = 0.08$). Patients' height did not show significant correlation with distance values.

3.2. Evaluation of distance *D* depending on the presence of joint effusion/intraarticular fluid mimicking arthroscopic irrigation fluid

Seventeen patients of the examined 61 showed minor to extensive joint effusion of the concerning knee joint. Also, within this subgroup, distance *D* was longer in 90°-flexion than in extended positioning of the knee (20.4 \pm 7.1 mm (9.8–34.2) vs. 13.7 \pm 4.0 mm (5.8–20.9), $p < 0.0001$). Of note, in both extended and 90°-flexed positioning, knee joints with effusion revealed significantly longer distances *D* in comparison to MRIs of knee joints without effusion (ext: 13.7 \pm 4.0 mm (5.8–20.9) vs. 10.3 \pm 3.9 mm (5.0–20.8), $p = 0.004$ and 90° flex: 20.4 \pm 7.1 mm (9.8–34.2) vs. 16.1 \pm 5.2 mm (8.2–34.5), $p = 0.012$, Table 2). Both subgroups (patients with joint effusion vs. patients without joint effusion) did not show significant differences according to age, weight, BMI and gender distribution. Figure 4 a-d shows an example of an MRI with extensive distension of the joint capsule in presence of a joint effusion.

3.3. Evaluation of portal safety depending on simulated lateral meniscal tear localization

Altogether, 2440 simulated suturing trajectory lines were drawn and analysed, 1220 each in extended and in 90°-flexion position, respectively. Of these 2440, a total of 973 (39.9%) transections were counted, 522 of 1220 (42.8%) in extended posi-

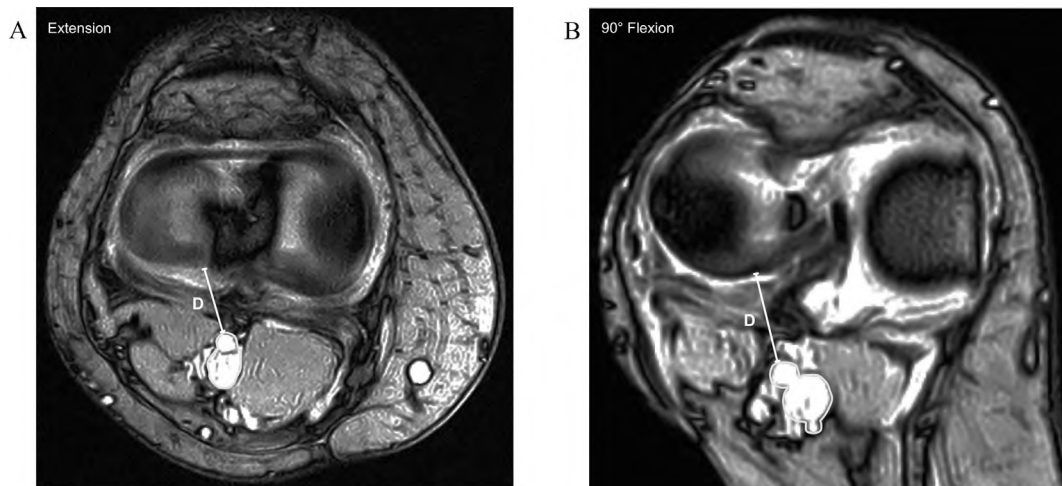


Figure 1. Evaluation of distance D. Axial T2 weighted Upright™ magnetic resonance imaging (MRI) of the knee joint at the level of the menisci (A) in extension and (B) in 90°-flexion positioning with assessment of distance D between the posterior horn of the lateral meniscus (PHLM) and the popliteal neurovascular bundle (pNVB). NVB is encircled in yellow and white line and letter D illustrate the distance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tion compared to 451 of 1220 (37.0%) in 90°-flexed knee joints. Regarding the distinct measurement points of the PHLM at increasing distance from the posterior cruciate ligament, at 0 mm, the 1 cm-lateral portal showed the fewest transections with 10 (16.4%) in extension and 5 (8.2%) in 90°-flexion (Tables 3 and 4). Yet, at 3 mm, 6 mm, 9 mm and 12 mm, the 1 cm-medial portal represented the safest arthroscopy portal with the fewest transections compared to the other simulated portals (Tables 3 and 4). At 12 mm, in both extension and flexion, the fewest transections were counted in comparison to the other measurement points.

According to distance *d* from the trajectory lines to the pNVB, at 0 mm, also the 1 cm-lateral portal was the safest in both extension and 90°-flexion position with an average *d* of 4.5 ± 3.7 mm (0–19.0, $p < 0.0001$) and 6.6 ± 4.6 mm (0–21.2, $p < 0.0001$, Tables 3 and 4). The 1 cm-medial portal was the safest portal in both extended and flexed knee position at 3 mm, 6 mm, 9 mm, 12 mm from the PCL with 3.7 ± 3.9 mm (0–16.6, $p = 0.004$), 6.0 ± 4.8 mm (0–19.4, $p < 0.0001$), 8.8 ± 5.2 mm (0–23.5, $p < 0.0001$) and 11.7 ± 5.4 mm (0–27.7, $p < 0.0001$) in extension and 7.2 ± 4.2 mm (0–17.5, $p < 0.0001$), 10.1 ± 4.6 mm (0–21.6, $p < 0.0001$), 13.1 ± 5.1 mm (0–25.1, $p < 0.0001$) and 16.6 ± 5.2 mm (0–29.3, $p < 0.0001$) in 90°-flexion, respectively (Tables 3 and 4).

4. Discussion

With this study we could demonstrate that the risk of injury of the popliteal neurovascular bundle during all-inside suturing of the posterior horn of the lateral meniscus as indicated by the measured distance between these anatomic structures decreases in 90°-flexion position, in presence of intraarticular fluid within the knee joint and with male gender and higher BMI/body weight values. Our analysis also revealed that selection of a safe arthroscopy portal to perform meniscal suturing depends on the localization of the meniscal tear in both extended and flexed position. A more lateral portal is safer when planning to suture the PHLM in close proximity to the PCL, whereas a more medial portal is safer when suturing the PHLM in a distance ≥ 3 mm lateral to the PCL.

In an attempt to determine high-risk patient groups for neurovascular injury during all-inside suturing of the lateral meniscus, previous studies have evaluated the relation between anatomical proximity of the lateral meniscus and the pNVB and patient demographic aspects [12–15,21]. It was proposed that patients of younger age, also during adolescence, and female gender encounter a greater risk of injury as these characteristics correlated with shorter distances to the neurovascular bundle, yet with regards to height, weight and BMI so far, no correlation could be demonstrated [12–15,21]. In the present study, correlation analysis also revealed significantly shorter distances between the PHLM and the pNVB in patients with female gender and younger age (of the latter only in the subgroup with extended knee joint) and we could thus confirm these cohorts to possibly represent high-risk groups. We found no association to patients' height. However, our analysis revealed shorter distances to be significantly related to patients' lower weight and BMI values suggesting that the popliteal vessels might shift backwards depending on the volume of the surrounding soft tissue [11].

Following up on this approach, it has been assumed that the popliteal neurovascular structures displace dorsally as the knee joint is bended [12,16,19,22,23]. So far, among early contradictory results [24], few cadaveric or MRI based studies proposed a higher neurovascular safety for all-inside suturing of the lateral meniscus with increasing flexion angle up to 90° of the knee measured either as distance from a simulated device trajectory or the posterior joint capsule to the pNVB

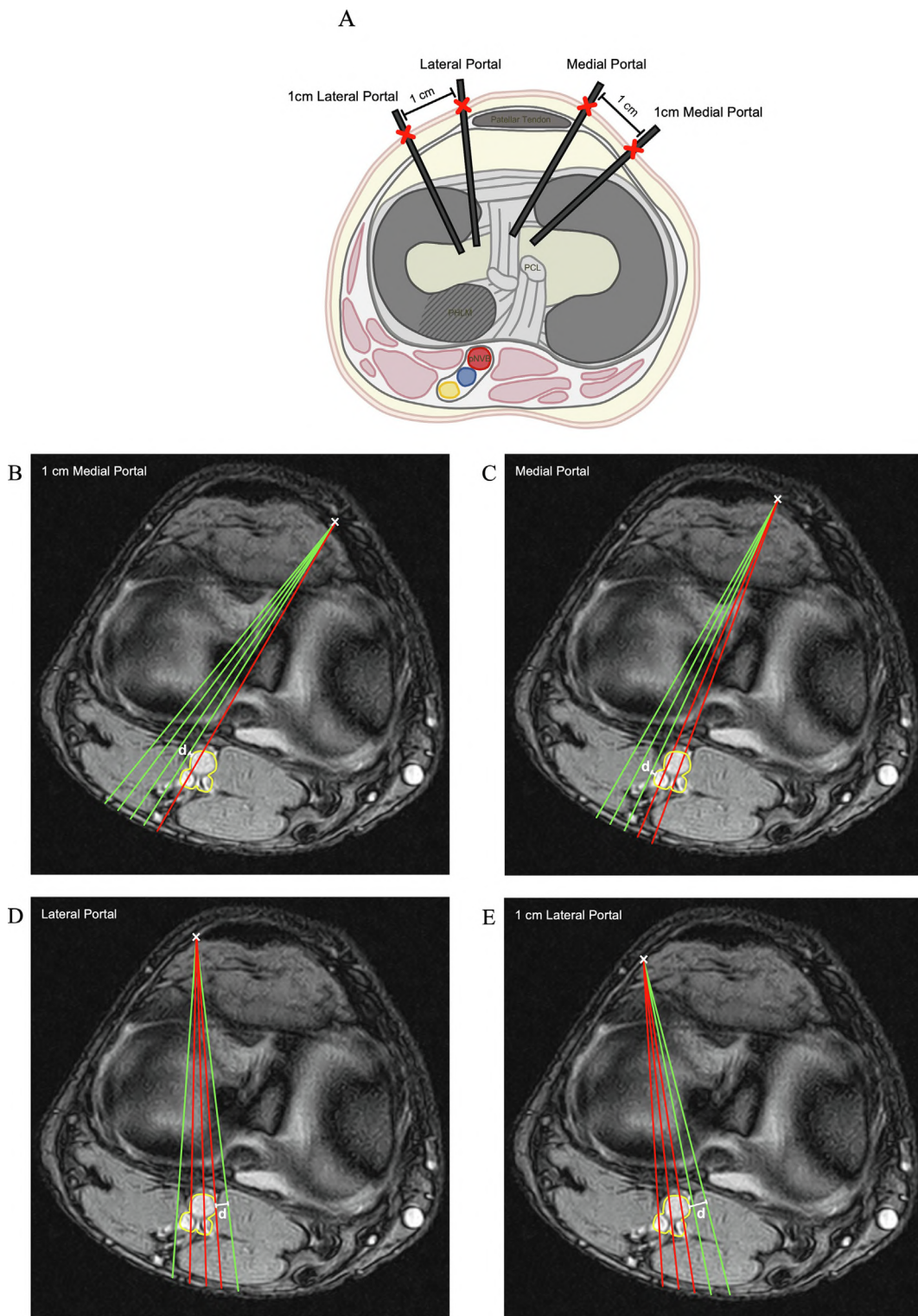


Figure 2. Evaluation of distance *d* for arthroscopy portal safety analysis. (A) Illustration of arthroscopy portal localization with one each at the medial and lateral edges of the patellar tendon and 1 cm further medial and 1 cm further lateral, respectively (1 cm-medial, medial, lateral and 1 cm-lateral portal). (B-E) Axial T2 weighted Upright™ magnetic resonance imaging (MRI) as an example of the extended knee joint at the level of the menisci with simulated all-inside suturing device trajectory lines from the distinct portal entry points to the posterior horn of the lateral meniscus (PHLM) at increasing distance from the posterior cruciate ligament (PCL; 0 mm, 3 mm, 6 mm, 9 mm, 12 mm). (B) 1 cm-medial portal (C) Medial portal (D) Lateral portal and (E) 1 cm-lateral portal. Green simulated trajectory lines illustrate safe passage of the popliteal neurovascular bundle (pNVB) and red trajectory lines signify transection of the NVB. White line and letter *d* illustrate the distance from each of the trajectory lines to the pNVB. The pNVB is encircled in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

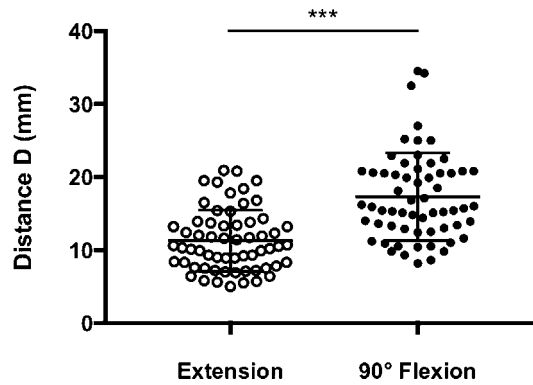


Figure 3. Comparison of distance D between MRIs of knee joints in extension and 90°-flexion as determined from the posterior horn of the lateral meniscus (PHLM) to the popliteal neurovascular bundle (pNVB). Dots show individual values of each measurement. *** $p < 0.0001$ as determined by paired student's t-test.

[12,16,23]. Average distance values varied from 1.0 mm to 9.6 mm in extension and from 8.6 mm to 13 mm in 90°-flexion position [12,15,16,21,23]. In line with these findings, intraindividual comparison of upright MRI scans in the present study revealed a significantly longer average distance between the popliteal vessels and the posterior border of the lateral meniscus of 17.3 mm in 90°-flexion position in comparison to 11.3 mm in extended knee joints. Thus, as usually performed, a figure-of-four position seems mandatory for sutures of the PHLM. The wide range among the above absolute distance values might be caused by different measurement approaches or patient selection. Furthermore, and in contrast to previous works, our study included MRI scans with joint effusion. As an additional means to improve arthroscopic safety by modifying the intraoperative setting, we hypothesized that the presence of joint effusion and thus intraarticular fluid to mimic arthroscopic irrigation fluid might further distend the joint capsule and thus displace the pNVB and increase the distance to the PHLM. We could support this assumption as patients with joint effusion showed significantly longer distances to the pNVB than the subgroup without joint effusion. As a possible consequence, the surgeon should always provide for a sufficient volume of irrigation fluid when performing sutures of the PHLM. Taking this into account by analysing selectively the subgroup of patients with joint effusion with their knee upright MRI scans in 90°-flexion position, an average distance of 20.4 mm, yet with a range of 10 to 34 mm might serve as a reference safety depth for insertion of suturing devices. Previous studies suggested a 15 mm penetration depth limiter for suturing devices. Considering that the needle of the device also penetrates the meniscus width, these recommendations seem reasonable [25,26]. Yet, one should consider that the meniscus might displace when applying pressure with suturing device and also, this value was determined independent of device penetration angles according to arthroscopy portals and the shape of the device tip. In order to address this aspect, we analysed the safety of all-inside suturing of the PHLM dependent on the choice of the arthroscopy portal and the localization of the meniscal tear. Previous cadaveric or MRI based studies suggested the anteromedial portal to be generally safer when suturing the PHLM, yet mainly tears ≥ 5 mm lateral to the PCL have been analysed [12,17,27,28]. Gilat et al. studied MRI scans in extension position and included assessment of PHLM tears in direct proximity to the PCL [13]. In line with these data, we could confirm in both extension and more importantly in 90°-flexion position, that for meniscal tears at 0 mm from the PCL the 1 cm-lateral portal was the safest, whereas in line with preliminary data tears ≥ 3 mm lateral to the PCL are more safely sutured from the 1 cm-medial portal. This could be demonstrated both by measuring the anatomical distance and assessing the absolute number of simulated transections. As a practical consequence, when using curved suture devices, the surgeon should consider turning the tip towards the PCL in case of tears in direct proximity to the PCL, whereas it should be turned the opposite direction when addressing tears ≥ 3 mm lateral to the PCL via an anteromedial portal [12,13].

Based on this demonstrated great importance of tear localization, a safe suturing of the PHLM implicitly demands for a detailed individual preoperative planning, especially - as mentioned before - in young, female patients with low BMI/weight. For acquiring this preoperative preparation in 90°-flexion position, upright MRI represents an excellent device to perform exact planning prior to surgery and thus optimally limit neurovascular risks during all-inside suturing of the PHLM.

Table 2

Comparison of distance D between patient-subgroups with and without knee joint effusion in extension and 90°-flexion.

Position of knee joint	Distance D to pNVB in mm (mean \pm SD, range)		p-value
	Effusion	No effusion	
Extension	13.7 \pm 4.0 (5.8–20.9)	10.3 \pm 3.9 (5.0–20.8)	0.004
90°-Flexion	20.4 \pm 7.1 (9.8–34.2)	16.1 \pm 5.2 (8.2–34.5)	0.012

Distance D is defined as the shortest distance between the posterior border of the posterior horn of the lateral meniscus (PHLM) and the most anterior point of the popliteal neurovascular bundle (NVB) in millimetres.

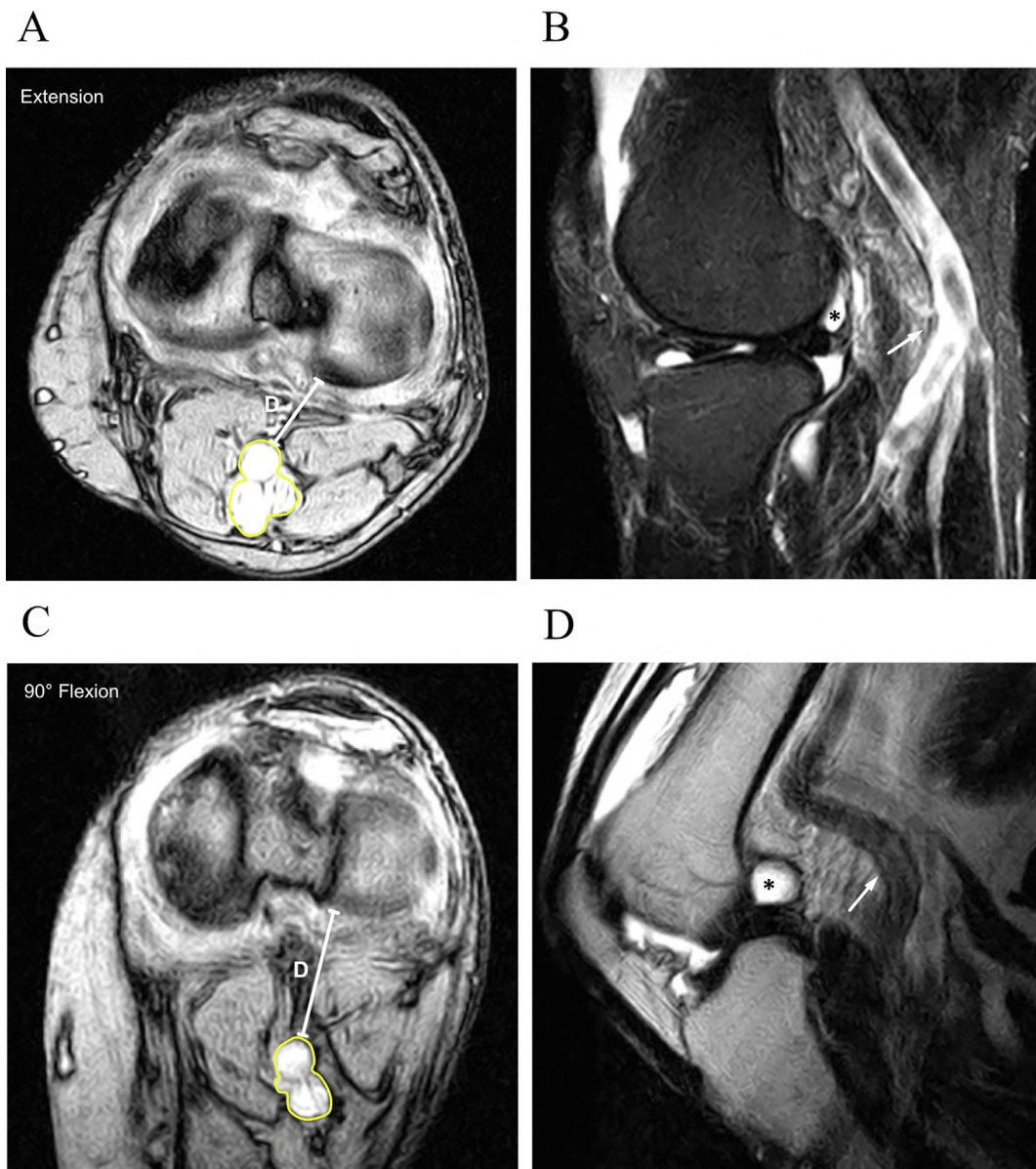


Figure 4. MRI scans with knee joint effusion, distension of the joint capsule and backshift of the pNVB. Upright™ magnetic resonance imaging (MRI) of a knee joint with (A and B) axial T2 weighted and sagittal STIR sequence in extended position and (C and D) axial and sagittal T2 weighted MRI scans in 90°-flexion position. Assessment of distance D between the posterior horn of the lateral meniscus (PHLM) and the popliteal neurovascular bundle (pNVB). NVB is encircled in yellow and white line and letter D illustrate the distance. White arrows illustrate shifting of the pNVB, black asterisk shows joint capsule distension. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3

Distance d/transsections of simulated trajectories in *Extension*, stratified to distinct portals and increasing positions from the PCL.

Position of simulated trajectory from PCL	Distance d of trajectory to pNVB in mm / Number of transections in extended knees (mean ± SD, range/n)				p-value
	1 cm-Medial Portal	Medial Portal	Lateral Portal	1 cm-Lateral Portal	
0 mm	2.0 ± 3.0 (0–13.2) / 31	0.8 ± 2.0 (0–10.5) / 45	2.4 ± 3.1 (0–16.5) / 25	4.5 ± 3.7 (0–19.0) / 10	<0.0001
3 mm	3.7 ± 3.9 (0–16.6) / 18	1.9 ± 3.2 (0–14.2) / 33	0.9 ± 2.1 (0–12.0) / 45	1.6 ± 2.6 (0–15.1) / 29	0.004
6 mm	6.0 ± 4.8 (0–19.4) / 7	4.1 ± 4.3 (0–17.7) / 19	0.5 ± 1.8 (0–8.9) / 52	0.6 ± 1.8 (0–10.6) / 51	<0.0001
9 mm	8.8 ± 5.2 (0–23.5) / 3	6.9 ± 5.0 (0–21.8) / 5	1.4 ± 2.8 (0–13.8) / 41	0.8 ± 2.1 (0–11.2) / 48	<0.0001
12 mm	11.7 ± 5.4 (0–27.7) / 1	10.2 ± 5.3 (0–25.7) / 1	3.5 ± 4.1 (0–18.3) / 23	2.0 ± 3.6 (0–15.8) / 35	<0.0001

Farthest d and fewest transections and thus safest portal for each position are typed bold. NVB, neurovascular bundle; PCL, posterior cruciate ligament.

Table 4

Distance d/transsections of simulated trajectories in 90°-flexion, stratified to distinct portals and increasing positions from the PCL.

Position of simulated trajectory from PCL	Distance d of trajectory to pNVB in mm / Number of transsections in 90° flexion (mean ± SD, range/n)				p-value
	1 cm-Medial Portal	Medial Portal	Lateral Portal	1 cm-Lateral Portal	
0 mm	4.1 ± 3.8 (0–13.4) / 11	1.2 ± 2.2 (0–9.6) / 36	2.8 ± 3.5 (0–13.2) / 25	6.6 ± 4.6 (0–21.2) / 5	<0.0001
3 mm	7.2 ± 4.2 (0–17.5) / 4	3.4 ± 3.5 (0–11.5) / 15	0.7 ± 1.9 (0–7.7) / 48	2.7 ± 3.6 (0–13.4) / 27	<0.0001
6 mm	10.1 ± 4.6 (0–21.6) / 0	6.6 ± 4.3 (0–15.3) / 5	0.4 ± 1.4 (0–7.4) / 55	0.9 ± 2.2 (0–9.9) / 49	<0.0001
9 mm	13.1 ± 5.1 (0–25.1) / 1	10.2 ± 4.6 (0–20.2) / 1	0.9 ± 2.1 (0–11.1) / 44	0.5 ± 1.7 (0–11.7) / 53	<0.0001
12 mm	16.6 ± 5.2 (0–29.3) / 1	14.0 ± 4.7 (0–23.9) / 1	3.0 ± 3.8 (0–16.1) / 26	1.3 ± 2.8 (0–13.9) / 44	<0.0001

Farthest d and fewest transsections and thus safest portal for each position are typed bold. NVB, neurovascular bundle; PCL, posterior cruciate ligament.

4.1. Limitations

The present study certainly has several limitations. Firstly and most important, as the upright MRI scanner is a 0.6 tesla magnet, image resolution was partially restricted in comparison to non-positional MRI scans which might have affected measurement accuracy. Secondly, joint effusion was evaluated only semi-quantitatively and other intraoperative variables like the impact of gravity or the applied varus force in the figure-of-four position could not be considered. Nevertheless, these aspects should not affect the major conclusions drawn from these results.

4.2. Conclusions

All-inside suturing of the PHLM is safer in 90°-flexion position, in presence of intraarticular fluid and in male patients with increasing weight/BMI and age. Sutures of the PHLM at 0 mm from the PCL are safer from a very lateral arthroscopic portal whereas for tears which are located ≥ 3 mm from the PCL a very medial portal involves a lower risk for the pNVB. Upright MRI represents an excellent device for preoperative planning to optimally minimize neurovascular risks.

Informed CONSENT

Informed consent was obtained from all patients included in the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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