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Published in: Journal of Orthopaedic Trauma

DOI:

10.1097/BOT.0000000000002043

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date: 2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Bleeker, N. J., Reininga, I. H. F., van de Wall, B. J. M., Hendrickx, L. A. M., Beeres, F. J. P., Duis, K. T., Doornberg, J. N., Jaarsma, R. L., Kerkhoffs, G. M. M. J., & IJpma, F. F. A. (2021). Difference in Pain, Complication Rates, and Clinical Outcomes After Suprapatellar Versus Infrapatellar Nailing for Tibia Fractures? A Systematic Review of 1447 Patients. *Journal of Orthopaedic Trauma*, *35*(8), 391-400. https://doi.org/10.1097/BOT.000000000000002043

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Difference in Pain, Complication Rates, and Clinical Outcomes After Suprapatellar Versus Infrapatellar Nailing for Tibia Fractures? A Systematic Review of 1447 Patients

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Objectives: To assess the effectiveness of suprapatellar (SP)-nailing versus infrapatellar (IP)-nailing of tibia fractures in anterior knee pain, complications (retropatellar chondropathy, infection, and malalignment) and physical functioning and quality of life. A clinical question-driven and thorough systematic review of current literature is provided.

Data source: PubMed and Embase databases were searched for studies published between 2010 and 2020 relating to SP and IP-nailing of tibia fractures. The study is performed in concordance with PRISMA-guidelines.

Study selection: Studies eligible for inclusion were randomized controlled trials, prospective and retrospective observational studies reporting on outcomes of interest.

Data extraction: Data extraction was performed independently by 2 assessors. Methodological quality and risk of bias was assessed according to the guidelines of the McMaster Critical Appraisal.

Data synthesis: Continuous variables are presented as means with SD and dichotomous variables as frequency and percentages. The weighted mean, standardized weighted mean differences, and 95% confidence

interval were calculated. A pooled analysis could not be performed because of differences in outcome measures, time-points, and heterogeneity.

Results: Fourteen studies with 1447 patients were analyzed. The weighted incidence of anterior knee pain was 29% after SP-nailing and 39% after IP-nailing, without reported significance. There was a significant lower rate of malalignment after the SP-approach (4% vs. 26%) with small absolute differences in all planes. No substantial differences were observed in retropatellar chondropathy, infection, physical functioning, and quality of life.

Conclusions: This systematic review does not reveal superiority of either technique in any of the respective outcomes of interest. Definitive choice should depend on the surgeon's experience and available resources.

Key Words: intramedullary nailing, tibia fractures, suprapatellar, infrapatellar, anterior knee pain, complications, physical functioning, general quality of life

Level of Evidence: Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

(J Orthop Trauma 2021;35:391-400)

Accepted for publication December 15, 2020.

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The authors report no conflict of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jorthotrauma.com).

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DOI: 10.1097/BOT.0000000000002043

INTRODUCTION

The number of good quality studies evaluating suprapatellar (SP) nailing of tibia fractures is rising, and the SP-approach gained popularity in the field of orthopaedic trauma as an alternative surgical approach for tibia fractures. The SP-approach was first described by Tornetta et al^{1,2} and a modified technique was described by Cole³ in 2006. Early reports suggest potentially less anterior knee pain as the main advantage, with incidences up to 71% reported after traditional infrapatellar (IP) approach.^{4–7} Second, straightforward positioning with less flexion of the knee may lead to better alignment control and lower rates of malalignment.^{8–10} On the contrary, the SP-approach may lead to iatrogenic damage of the intra-articular structures of the knee^{11–15} and potentially an increased risk for infection,^{16,17} because the nail will be introduced superior of the proximal patellar pole and passes the articular surface.

The potential superiority of SP-approach for intramedullary nailing (IMN) of the tibia is subject of ongoing debate. Since its introduction, early results were considered to be promising in anterior knee pain, 23–26 optimal

alignment control, 8-10,14,24 physical functioning, 23,24,26 and general quality of life (QoL). 23,26,27 However, other studies found no differences in anterior knee pain and functional outcomes if compared to IP-nailing. 10,12,28 Furthermore, data on theoretical concerns regarding retropatellar chondropathy and infection rates after the SP versus IP-approach are scarce. The most recent systematic review on this subject was published in 2019 in this Journal²⁰ and concluded that the SP-approach results in less pain and better functional outcomes if compared with IP-approach. The literature search of this systematic review was performed until august 2018, and resulted in the inclusion of 5 studies. However, over the last decade, several more good quality studies [both randomized controlled trials (RCT's) and cohort studies] reporting on pain, complications, physical functioning, and general QoL were published on SP versus IP-approach for nailing of tibia fractures that improves our understanding and contribute to the ongoing debate.

Therefore, this systematic review on SP versus IP-nailing provides an update with inclusion of these additional studies with the aim of answering the following clinical research questions: (1) does the SP versus IP-approach result in less anterior knee pain?; (2) does the SP versus IP-approach influence complication rates (retropatellar chondropathy, infection, malalignment, nonunion, and subsequent surgeries)?; and (3) does the SP versus IP-approach affect physical functioning and QoL?

MATERIAL AND METHODS

This systematic review was conducted and written in concordance with the Preferred Reporting Items for Systematic Reviews (PRISMA).²⁹ The protocol of this systematic review is registered in the international PROSPEROdatabase (CRD42020181854).

Objectives and Study Sources

The PubMed and Embase databases were searched on 23-04-2020 for articles published between 2010 and 2020 relating to tibia fractures, IMN, and nailing technique (SP and IP). A medical librarian constructed the search strategy, which is presented in **Supplemental Digital Content 1** (see **Table**, http://links.lww.com/JOT/B319).

Study Selection

Studies eligible for inclusion were RCT's, prospective and retrospective observational studies reporting on: (1) tibia fractures; (2) IMN; (3) nailing technique; (4) anterior knee pain; (5) complications [retropatellar chondropathy, infection, malalignment, non-union, subsequent surgeries and range of motion (ROM)]; (6) physical functioning and QoL, assessed with patient-reported outcome measures (PROMs); (7) minimal follow-up of 6 months; and (8) patient's age ≥18 years. Studies were excluded in case of: (1) pediatric fractures; (2) animal studies; (3) case reports, conference abstracts, systematic reviews or meta-analyses; (4) surgical treatment other than IMN; and (5) language other than English, German, Dutch, French and Spanish.

Study selection was executed in duplicate by N.J.B. and F. IJ. and performed in 2 stages with use of Rayyan

software.³⁰ In stage 1, title and abstract were screened. In stage 2, full text screening was performed. Disagreement was resolved by discussion according to the Cochrane Handbook for Systematic Reviews of Interventions.²⁹

Data Extraction

Methodological quality and risk of bias of included studies was independently assessed by N.J.B. and I.H.F.R. according to the guidelines of the McMaster University Occupational Therapy Evidence-Based Practice Research Group.³¹ The McMaster critical appraisal consists of 8 categories including: (1) study purpose; (2) literature review; (3) study design; (4) study sample; (5) study outcome; (6) study intervention; (7) study results; and (8) conclusions and implications. Scores included: "yes = 1 point," "no = 0 points," "not addressed (N/A)," and "not applicable (NA)." The total score reflects the methodological quality with a maximum score of 16 for RCT's and 14 for other designs. The definitive score may vary from 0% to 100%, with a higher score indicating a higher methodological quality. Scores between 75% and 89% indicated good-quality studies and scores between 90% and 100% indicated excellent-quality studies. Based on the quality of the studies, a best-evidence synthesis was performed. Any continued disagreements were solved during a consensus meeting with N.J.B., I.R., and F.F.A.I.

Data extraction was performed independently by N.J.B. and F.F.A.I. using a predefined extraction file. Patient demographics, study details, OTA/AO classification, ³² follow-up duration, and outcome measures of interest were extracted from included studies.

Surgical Technique

The SP-approach encompasses 2 surgical techniques described by respectively Ryan³³ and Sanders et al¹⁴ Ryan et al³³ describes an incision in the midline to the superior pole of the patella. Using this incision as a mobile window, a partial medial parapatellar arthrotomy is performed. The entry-point is reached by subluxating the patella laterally. The technique described by Sanders et al¹⁴ uses a longitudinal incision proximal of the superior pole of the patella. The entry point is reached by splitting the distal quadriceps and lifting the patella. The knee is 20–30 degrees flexed and potential damage to the intra-articular structures of the knee is avoided using a sleeve.³⁴ The entry point at the anteromedian side of the proximal tibia is determined under fluoroscopy assistance.³⁴

The traditional IP-approach encompasses 3 main surgical approaches distal of the inferior pole of the patella, including the medial parapatellar, lateral parapatellar, and tendon-splitting approach. The definitive choice depends on the surgeon's preference and is usually not reported on in studies. The knee is positioned in 90 degrees flexion. The longitudinal incision is made from the distal pole of the patella toward the tibia tubercle. The entry point for the intramedullary nail is equal to the SP-approach.

Definition(s) of Outcome Measures

Anterior knee pain is defined as discomfort located anteriorly of the affected knee, which occurred after tibia nailing. Anterior knee pain is presented as a percentage of patients experiencing knee pain, or objectified with use of PROMs. The PROMs reporting on pain are listed in **Supplemental Digital Content 2** (see **Supplemental Digital Content 2**, http://links.lww.com/JOT/B320).

Complications include retropatellar chondropathy, infection, malalignment, nonunion, subsequent surgeries, and impaired ROM of the knee joint. Retropatellar chondropathy is defined as iatrogenic damage to the patellofemoral joint after SP-nailing detected by peroperative arthroscopy and postoperative MRI of the knee. Infection is categorized into superficial and deep infections and encompassed septic arthritis.35 Malalignment is divided into angular deformities in the coronal or sagittal plane and rotational malalignment. Angular deformities are defined as a deformity of ≥ 5 degrees in the coronal or sagittal plane^{8,36,37} and rotational malalignment is defined as a rotation of ≥ 10 degrees in comparison to the unaffected side. 38,39 Nonunion includes no signs of cortical healing after 6 months. Subsequent surgeries include screw(s) removal, implant removal, and revision for complications. ROM is extracted as reported in included studies and includes the flexion and extension of the affected or/and unaffected knee joint.

PROMs encompassed multiple questionnaires reporting on 2 constructs, predefined for this study: (1) physical functioning; and (2) QoL. The different PROMs are described in **Supplemental Digital Content 2** (see **Supplemental Digital Content 2**, http://links.lww.com/JOT/B320).

Data Synthesis

Continuous variables are presented as means with SD and dichotomous variables as frequency and percentages. In case of more than 2 reported continuous variables in more than one group, the weighted mean and weighted SD was calculated. For dichotomous variables presented as frequency or percentage, the weighted mean frequency or percentage was calculated.

For comparative studies, the differences in continuous outcomes were calculated using the inverse variance weighting method and presented as standardized weighted mean difference (SMD) and 95% confidence interval (95% CI). Differences of dichotomous variables within comparative studies were calculated by use of the X²-test according to the Cochrane Handbook for Systematic Reviews of Interventions. ⁴⁰ *P*-values below 0.05 were considered to indicate statistical significance.

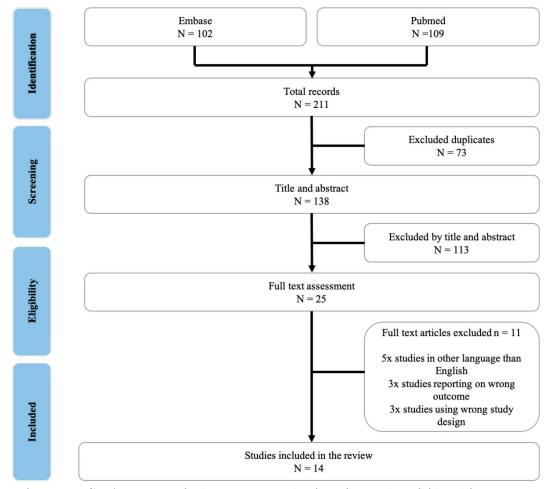


FIGURE 1. Search syntax. Editor's Note: A color image accompanies the online version of this article.

RESULTS

Search

The literature search resulted in 201 articles of which eventually 25 full-text articles were screened. A total of 14 studies met inclusion criteria and were eligible for further analysis (Fig. 1).8-10,12,14,16,17,23,24,27,28,41-43

Study Characteristics

A total of 1447 patients were included in this systematic review, including 760 fractures treated with the SP-technique and 700 fractures treated with the IP-technique (Table 1). Nine studies were comparative studies *\frac{8-10,12,16,27,28,41,43}{1,43} and 4 noncomparative studies reporting on either the SP-approach*\frac{14,17,23,24}{1,43} or IP-approach*\frac{42}{1,43}

Methodological Quality and Risk of Bias

There were 2 RCTs, 12,43 one prospective single cohort study, 14 7 retrospective comparative cohort series, 8-10,16,27,28,41 and 4 retrospective single cohort series. 17,23,24,42 The mean overall score of RCT's was 94 (SD 0) and of other designs 75 (SD 7), respectively.

The results of the methodological quality assessments are presented in **Supplemental Digital Content 3** (see **Table**, http://links.lww.com/JOT/B321).

Anterior Knee Pain

Eight studies reported on anterior knee pain, including 6 comparative studies ^{10,12,27,28,41,43} and 2 noncomparative studies (Table 2). ^{14,42} The weighted incidence of anterior knee pain was 29% after the SP-approach (range 0%–38%) ^{10,12,27} and 39% after the IP-approach (range 14%–46%). ^{10,12,27,42} No substantial differences were reported on Visual Analogue scale, Numeric Rating scale, and hospital special surgery score (HSS) pain scores & Lysholm pain scores for the SP-approach and IP-approach (Table 2).

Best-evidence synthesis showed that 5 of 8 studies that reported on knee pain were of good^{10,28,42} or excellent quality.^{12,43} MacDonald et al⁴³ reported a significant difference between the SP and IP-group in the AWT-K test after 12 months during fully weight-bear kneeling for 60 seconds. No other relevant differences were observed.

TABLE 1. Study Characteristics of Included Studies

						G ()	OTT 4 / 4 O		Follow-up‡ (Mean ± SD)	
Author	Year	Country	Design	N*	Period	Group(s) (n)†	OTA/AO- Classification	Outcomes	SP	IP
Avilucea et al ⁸	2016	USA	RSC	266	2008–2014	SP (132) vs. IP (134)	43-A, 43-C1, 43-C2	Complications	>6	>6
Cazatto et al ²³	2018	Italy	RSC	25	2014–2016	SP (25)	42-A, 42-B, 42-C	Complications, physical functioning, QoL	29 (6)	NR
Chan et al ¹²	2016	USA	RCT	25	2011–2012	SP (11) vs. IP (14)	42-A, 42-B, 42-C	Pain, complications, QoL	16 (5)	
Courtney et al ⁹	2015	USA	RSC	45	2009–2013	SP (21) vs. IP (24)	42-A, 42-B, 42-C	Complications, physical functioning	8 (8)	13 (10)
Cui et al ⁴¹	2019	China	RSC	50	2014–2016	SP (24) vs. IP (26)	42-A, 42-B, 42-C	Pain, physical functioning	24 (7)	23 (7)
Fu et al ²⁴	2016	China	RSC	23	2012–2013	SP (23)	41-A2, 41-A3, 42-A, 42-B, 42-C	Complications, physical functioning	16 (3)	NR
Isaac et al ²⁸	2019	USA	RSC	262	2011–2016	SP (91) vs. IP (171)	NR	Pain	43 (18)	50 (19)
Jones et al ¹⁰	2014	UK	RSC	74	NR	SP (36) vs. IP (38)	42-A, 42-B, 42-C	Pain, complications, physical functioning, QoL	23 (6)	28 (5)
Leliveld et al ⁴²	2012	NL	RSC	71	1998–2008	IP (72)	42-A, 42-B, 42-C	Pain, complications, physical functioning	NR	84 (37)
MacDonald et al ⁴³	2019	UK	RCT	95	2011–2013	SP (53) vs. IP (42)	NR	Pain, complications, physical functioning	>6	>6
Marecek et al ¹⁶	2018	USA	RSC	282	2009–2015	SP (147) vs. IP (142)	NR (open fractures)	Complications	9 (9)	11 (13)
Mitchell et al ¹⁷	2017	USA	RSC	135	2011–2016	SP (139)	NR (open fractures)	Complications	9 (13)	NR
Ozcan et al ²⁷	2020	Turkey	RSC	58	2010–2017	SP (21) vs. IP (37)	NR	Pain, physical functioning	16 (4)	33 (19)
Sanders et al ¹⁴	2014	USA	PSC	36	2007–2011	SP (37)	42-A, 42-B, 42-C	Pain, complications, physical functioning, QoL	19 (9)	NR

^{*}Total patients.

[†]Total fractures

[†] Follow-up in months

RSC, retrospective cohort; PSC, prospective cohort; NR, not reported.

Complications

Two studies reported on retropatellar chondropathy after the SP-approach. ^{12,14} Chan et al ¹² reported chondropathy in 3 of 11 (27%) patients based on pre- and post-SP-nailing arthroscopy. One had preexisting chondromalacia; one sustained small iatrogenic scratches of the trochlea, and one had some damage to the undersurface of the patella. All patients with post-SP-nail arthroscopic changes had a full recovery at 1-year follow-up. Sanders et al ¹⁴ reported grade II chondromalacia at the trochlea groove—probably because of pressure of insertion cannula—in 2 of 37 (5%) patients based on immediate arthroscopy after SP-nail insertion. Two patients exhibiting arthroscopic changes had normal MRIs at 1-year follow-up (Table 3).

Eight studies reported on infection, ^{12,14,16,17,23,24,42,43} including 3 good-quality studies ^{16,24,42} and 2 excellent-quality studies. ^{12,43} The weighted infection rate was 12% after the SP-approach (range 0%–18%) ^{12,14,16,17,23,24,43} and 9% after the IP-approach (range 0%–20%), ^{12,16,42,43} with most infections occurring after nailing of open fractures (SP 18% vs. IP 14%). ^{16,17} None of the patients included by Mitchell et al¹⁷ developed septic arthritis of the knee after the SP-approach, whereas Marecek et al¹⁶ reported 2 cases (1%) of 147 patients after the SP-approach.

Seven studies reported on alignment, 8-10,12,14,24,42 including 5 good- and excellent-quality studies. 8,10,12,24,42 Avilucea et al⁸ reported 15% malalignment (40 of 266 patients) in the overall study population, with a significant difference between SP-group (5 patients, 4%) and IP-group (35 patients, 26%) (P < 0.005). The mean difference in alignment in comparison to the unaffected side in the coronal plane after SP-nailing was 3.2 degrees (SD 1.1 degree) versus 5.7 degrees (SD 1.8 degrees) after IP-nailing (SMD -1.7 degrees). The mean difference alignment in the sagittal plane was 2.9 degrees (SD 1 degree) versus 5.5 degrees (SD 2.3 degrees) after the IP-approach (SMD -1.5 degrees). Rotational malalignment was not reported. Courtney et al⁹ reported significant differences in the sagittal plane (SMD) 0.6 degrees) and Jones et al¹⁰ reported significant differences in the coronal plane (SMD -0.6 degrees), both in favor of the SPapproach (Table 3).

Three studies reported on fracture healing ^{10,12,14} including one good-quality study¹⁰ and one excellent-quality study.¹² The incidence of nonunion based on measurements on plain radiographs ranged from 1% to 9% after SP-nailing ^{10,12,14} and was 0% after IP-nailing ^{10,12} and did not statistically differ between the SP- and IP-approach (Table 3).

Eight studies reported on subsequent surgeries, ^{10,12,14,16,23,24,42,43} of which 6 studies were of good-to excellent-quality. ^{10,12,16,24,42,43} The weighted rate of

TABLE 2. Anterior Knee Pain After SP and IP Approach for Nailing of Tibia Fractures

			-12 10	> n	P/SMD	
Study and Outcome	Groups (n)	SP	IP	SP	IP	[95% CI]
Anterior knee pain						-
Cases %						
Chan et al ¹²	SP (11) vs. IP (14)	NR	NR	0 (0%)	2 (14%)	P 0.3
Jones et al10	SP (36) vs. IP (38)	NR	NR	12 (33%)	16 (42%)	P 0.4
Leliveld et al42	IP (71)	NR	NR	NR	27 (38%)	NA
Ozcan et al ²⁷	SP (21) vs. IP (37)	NR	NR	8 (38%)	17 (46%)	P 0.6
VAS						
Chan et al ¹²	SP (11) vs. IP (14)	NR	NR	Mean 0.4	Mean 1.5	NA
MacDonald et al ⁴³	SP (53) vs. IP (42)	Mild 36; moderate 1; severe 0*	Mild 22; moderate 1; severe 0*	NR	NR	NA
Sanders et al14	SP (36)	NR	NR	0	NR	NA
Numeric Rating scale						
Isaac et al ²⁸	SP (91) vs. IP (171)	NR	NR	Kneeling 4 (4); resting 2 (3); walking 3 (3)	Kneeling 4 (4); resting 2 (3); walking 3 (3)	NA
AWT-K						
MacDonald et al43	SP (53) vs. IP (42)	$36/37^{1}$	$18/23^2$	NR	NR	NA
HSS pain score						
Cui et al ⁴¹	SP (24) vs. IP (26)	NR	NR	29 (2)	28 (3)	SMD 0.4 [-0.2 to 0.9]
Lysholm pain score						
Chan et al ¹²	SP (11) vs. IP (14)	NR	NR	24	20	NA
Sanders et al ¹⁴	SP (36)	NR	NR	22	NR	NA

Visual Analogue scale (0 (no pain)—10 (worst pain)), Numeric Rating scale (0 (no pain)—10 (worst pain)), AWT-K (Aberdeen weightbearing test)^{1,2} Proportion of patients who completed the AWT-K as secondary outcome measurer of the test. HSS pain score (0 (complete discomfort)—100 (no discomfort)), Lysholm pain score (0 (heavy pain)—25 (no pain)). *Mild (0–39), moderate (40–79), severe (80–100).

^{95%} CI, 95% confidence interval; NR, not reported, NA, not applicable.

 TABLE 3. Complications After SP- Versus IP-Nailing for Tibia Fractures

		Outco			
Complications	Study	SP	IP	P/SMD [95% CI]	
Retropatellar					
chondropathy cases (%)	GI 112	2 (250()	0 (00()	B 0.4	
	Chan et al ¹²	3 (27%)	0 (0%)	P 0.1	
	Sanders et al ¹⁴	2 (5%)	NR	NA	
infection cases (%)	. 122	0.7007	3.75		
	Cazatto et al ²³	0 (0%)	NR	NA	
	Chan et al ¹²	0 (0%)	0 (0%)	NA	
	Fu et al ²⁴	0 (0%)	NR	NA	
	Leliveld et al ⁴²	NR	Total 4 (6%); deep 1 (1%); superficial 3 (4%)	NA	
	MacDonald et al43	2 (4%)	0 (0%)	P 0.4	
	Marecek et al ¹⁶	Total 24 (16%); deep 16 (11%); superficial 8 (5%)	Total 20 (14%); deep 14 (10%); superficial 6 (4%)	P 0.6	
	Mitchell et al ¹⁷	Total 25 (18%); deep 16 (12%); superficial 9 (7%)	NR	NA	
	Sanders et al ¹⁴	2 (5%)	NR	NA	
Primary angular	Sunacis et ui	2 (370)	1110	11/1	
malalignment cases (%)					
	Avilucea et al ⁸	5 (4%)	35 (26%)	P < 0.005*	
	Chan et al ¹²	1 (not specified)		NA	
	Leliveld et al ⁴²	NR	3 (4%)	NA	
	Sanders et al ¹⁴	1 (3%)	NR	NA	
Mal)alignment coronal blane mean ± SD°					
	Avilucea et al ⁸	3.2 degrees (1.1 degree)	5.7 degrees (1.8 degrees)	SMD -1.7 degrees* [-2 to 1 degrees]	
	Courtney et al ⁹	2.5 degrees (1.9 degrees)	3.2 degrees (2.0°)	SMD -0.4 degrees [-0.9 to 0 degrees]	
	Fu et al ²⁴	1.6 degrees (1 degree)	NR	NA	
	Jones et al ¹⁰	1 degrees (0.8 degrees)	2 degrees (2.3 degrees)	SMD -0.6 degrees* [-1 to 0	
Mal)alignment sagittal				degree]	
plane mean ± SD°					
	Avilucea et al ⁸	2.9 degrees (1 degree)	5.5 degrees (2.3 degrees)	SMD -1.5 degrees* [-1.7 to 1.2 degrees]	
	Courtney et al ⁹	2.9 degrees (2.6 degrees)	4.6 degrees (2.7 degrees)	SMD 0.6 degrees* [-1.2 to 0 degrees]	
	Fu et al ²⁴	2.1 degree (1.3 degrees)	NR	NA	
	Jones et al ¹⁰	0 degrees (2.2 degrees)	0° (5.2 degrees)	SMD 0 degrees [-0.5 to 0.5	
				degrees]	
Rotational (mal)alignment					
cortical width(s) in mm	C 10	0.2 (0.4)	0.2 (0.2)	CD CD 0.2.5 0.4 1 0.01	
	Courtney et al ⁹	0.3 (0.4)	0.3 (0.3)	SMD $0.2 [-0.4 \text{ to } 0.8]$	
Non-union cases (%)	cr 112	1 (00)	0 (00)	5.04	
	Chan et al ¹²	1 (9%)	0 (0%)	P 0.4	
	Jones et al ¹⁰	1 (1%)	0 (0%)	P 0.5	
Subsequent surgeries cases (%)	Sanders et al ¹⁴	1 (3%)	NR	NA	
Jases (70)	Cazatto et al ²³	6 (24%)	NR	NA	
	Chan et al ¹²	1 (9%)	0 (0%)	P 0.4	
	Fu et al ²⁴	1 (48%)	0 (0%) NR	NA	
	Jones et al ¹⁰	11 (48%)	0 (0%)	P 0.5	
	Leliveld and	1 (3%) NR	44 (62%)	P 0.5 NA	
	Verhofstad ⁴²	INK	77 (0270)	INA	
	MacDonald et al43	13 (25%)	4 (10%)	P 0.1	

		Outco			
Complications	Study	SP	IP	P/SMD [95% CI]	
	Marecek et al16	28 (19%)	30 (21%)	P 0.7	
	Sanders et al14	7 (19%)	NR	NA	
ROM F/E (flexion/ extension) mean arc ± SD					
	Chan et al ¹²	F/E affected side 131 degrees/ 0.4 degrees	F/E affected side 137 degrees/ 0.8 degrees	NA	
		F/E unaffected side 129 degrees/0.4 degrees	F/E unaffected side 138 degrees/0.8 degrees		
	Fu ²⁴	117.9 degrees (5.31 degrees)	NR	NA	
	Sanders et al ¹⁴	Affected side 124.2 degrees (SD NR)	NR	NA	
		Unaffected side 127.2 degrees (SD NR)			

TABLE 3. (Continued) Complications After SP- Versus IP-Nailing for Tibia Fractures

*Statistically significant.

NR, not reported; NA, not applicable.

subsequent surgeries was 21% after the SP-approach (range 3%–48%)^{10,12,14,16,23,24,43} and 26% after the IP-approach (range 0%–62%).^{10,12,16,42,43} None of the comparative studies^{10,12,16,43} showed significant differences in rates of subsequent surgeries. A specification of subsequent surgeries is presented in **Supplemental Digital Content 4** (see **Table**, http://links.lww.com/JOT/B322).

Three studies reported on ROM (Table 3) 12,14,24 including one good-quality study 24 and one excellent-quality study. 12

Fu et al²⁴ reported a significant difference between ROM preoperatively and postoperatively at last follow-up after SP-approach (26.7 vs. 117.9 degrees). Other studies reported no substantial differences in knee ROM between the affected and unaffected side at clinical follow-up (Table 3).^{12,14}

Physical Functioning and General Quality of Life

Ten studies reported on physical functioning of the knee, 9,10,12,14,23,24,27,41-43 of which 5 studies were of good or excellent quality. 10,12,24,42,43 Only MacDonald et al⁴³ determined a statistically significant difference in Lysholm scores after 12 months between the SP and IP-approach (SMD 0.6) (Table 4). There were no differences observed with almost equal outcomes for the SP and IP-approach in international knee documentation committee (IKDC), Oxford knee score (OKS), Kujala Knee score, HSS, Olerud-Molander Ankle score (OMAS), and Irrgang scores (Table 4).

Four studies reported on general $QoL^{10,12,14,23}$ including 2 studies with good or excellent methodological quality. No relevant differences were observed in SF-36 and SF-12 scores between the SP and IP-approach.

DISCUSSION

The rationale for choosing an SP instead of IP approach for IMN of tibial fractures is potentially less anterior knee

pain. Clinical concerns of the SP-approach, however, may include iatrogenic damage to articular cartilage^{11,13–15} and infection. ^{16,17} This is the first systematic review in which inclusion criteria were not limited by study design and that provides a comprehensive overview of current literature published over the last decade regarding complete spectrum of outcomes measures following SP or IP-nailing for tibia fractures.

This systematic review found no substantial decrease in the incidence of anterior knee pain regarding the SP- versus IP-approach (29% vs. 39%). In complications, only the rate of malalignment was significantly different (4% vs. 26%) with small absolute differences in the coronal and sagittal plane in favor of the SP-approach. No differences were observed in risk on retropatellar chondropathy, infection, nonunion, and subsequent surgeries. Self-reported physical functioning and QoL were comparable in both groups.

Does the SP Versus IP-Technique Result in Less Anterior Knee Pain?

The weighted incidence of anterior knee pain among studies after SP-nailing was 29% versus 39% after IPnailing. There was a higher rate of anterior knee pain after IP-nailing; however, the studies that compared outcomes after SP to IP-nailing^{10,12,27} reported no significant differences. The incidence of anterior knee pain ranged from 0% to 38% after SP-nailing and 14%-46% after IP-nailing. 10,12,27,42 The wide range may be explained by the multifactorial nature of anterior knee pain. Etiologies may include iatrogenic damage to the IP nerve, 42 to Hoffa's fat pad, 44 periosteal irritation of the entry point, patellar tendinopathy, or nail prominence.⁴⁵ Moreover, knee pain persists after nail removal in up to 60% of the cases. 5,42,46 It may be noteworthy that the IP-approach is used for implant removal, even after initial SP-nailing. Further research is needed to clarify the etiology of anterior knee pain and elucidate pain perception.

TABLE 4. Physical Functioning and QoL After the SP Approach Versus the IP Approach

Study and			-12 no	>12 mo		D/CMD 1050/
Study and Outcome	Group(s)	SP	IP	SP	IP	<i>P</i> /SMD [95% CI]
Physical functioning						
IKDC						
Cazatto et al ²³	SP (25)	NR	NR	77 (6)	NR	NA
OKS						
Cazatto et al ²³	SP (25)	NR	NR	42 (6)	NR	NA
Courtney et al ⁹	SP (21) vs. IP (24)	36 (12)	40 (9)	NR	NR	SMD -0.4 [-0.9 to 0.2]
Kujala score						[*** ** **=]
Cazatto et al ²³	SP (25)	NR	NR	85 (4)	NR	NA
Jones et al ¹⁰	SP (36) vs. IP (38)	NR	NR	68 (23)	75 (19)	SMD 0.3 [-0.8 to 0.1]
Leliveld and Verhofstad ⁴²	IP (71)	NR	NR	NR	83 (16)	NA
Ozcan et al ²⁷	SP (21) vs. IP (37)	NR	NR	80 (9)	83 (8)	SMD -0.4 [-0.9 to 0.2]
Lysholm score						
Chan et al ¹²	SP (11) vs. IP (14)	NR	NR	98	86	NA
Cazatto et al ²³	SP (25)	NR	NR	99 (7)	NR	NA
MacDonald et al ⁴³	SP (53) vs. IP (42)	93 (11)	84 (20)	NR	NR	SMD 0.6* [-0.2 to 1]
Ozcan et al ²⁷	SP (21) vs. IP (37)	NR	NR	85 (8)	83 (8)	SMD 0.3 [-0.3 to 0.8]
Sanders et al ¹⁴	SP (36)	NR	NR	Excellent 14; good 8; fair 7; poor 8; * mean 82.2	NR	NA
HSS						
Cui et al ⁴¹	SP (24) vs. IP (26)	NR	NR	97 (5)	97 (6)	SMD 0 [-0.5 to 0.5]
Fu^{24}	SP (23)	NR	NR	92 (4)	NR	NA
OMAS						
Fu et al 2016 ²⁴ Irrgang	SP (23)	NR	NR	94 (4)	NR	NA
MacDonald et al ⁴³	SP (53) vs. IP (42)	Total 73 (8); symptoms 32 (4); function 41 (6)	Total 68 (13); symptoms 30 (7); function 38 (7)	NR	NR	SMD 0.5 [0.1 to 0.9]
QoL						
SF-36						
Cazatto et al ²³	SP (25)	NR	NR	79 (6)	NR	NA
Chan et al ¹²	SP (11) vs. IP (14)	NR	NR	PCS 46	PCS 38	NA
				MCS 47	MCS 47	
Sanders et al ¹⁴	SP (36)	NR	NR	PCS 42		
				MCS 48	NR	NA
SF-12						
Jones et al ¹⁰	SP (36) vs. IP (38)	NR	NE	PCS 40 (13)	PCS 43 (12)	SMD -0.2 [-0.7 to 0.2]
				MCS 49 (12)	MCS 51 (9)	SMD 0.2 [-0.3 to 0.6]

IKDC (scale 0-100, 100 = no pain, no limitations in sports and daily activities), OKS (scale 0-48, 48 = no restrictions in terms of pain and function) Kujala Knee score (scale 0-100, 100 = excellent physical functioning) Lysholm Knee score (scale 0-100, 100 = no disability) HSS (scale 0-100, 100 = no discomfort) OMAS (scale 0-100, 100 = no symptoms and normal physical functioning) Irrgang (scale 0-80, 80 = no symptoms and excellent function) SF-36 (short-form 36), SF-12 (short-form 12), physical component scale (PCS), mental component scale (MCS).

^{*}Excellent 95–100, good 84–94, fair 65–83, poor <65.

NR = not reported, NA = not applicable.

Does the SP- Versus IP-Technique Influence Complication Rates?

Another concern that may arise with SP-nailing is potential iatrogenic damage to intra-articular structures and cartilage as the nail passes the knee-joint.^{2,3,34} Several cadaveric studies reported conflicting results.^{13,15,47} Only Sanders et al¹⁴ and Chan et al¹² reported on clinical evaluation of retropatellar chondropathy after SP-nailing with an average follow-up of 16 and 19 months, respectively. They found hardly any cartilage damage, gouges, or pressure changes from the SP-nail insertion cannula in the patellofemoral joint based on per-operative arthroscopy and MRI after 12-months. However, good-quality long-term data are limited, which may improve our understanding regarding this clinical concern.

The infection rates after the SP-approach and IP-approach were comparable and showed no relevant differences (12% vs. 9%). Most infections occurred after nailing of open fractures with comparable rates following SP or IP-nailing, indicating that open fractures are more decisive for infection instead of the nailing technique. The chance on developing knee sepsis after SP-nailing of open fractures was considerably low in comparison to IP-nailing. 16,17

There is low evidence that SP-nailing leads to lower rates of malalignment. The current review showed significant differences in malalignment in the sagittal and coronal plane in favor of the SP-technique.^{8–10} SP-nailing may be beneficial in facilitating reduction and obtaining accurate alignment in more proximal- and distal tibia fractures¹⁴ as showed by Avilucea et al8 who assessed distal tibia fractures. Fu et al24 included proximal and distal tibia fractures, but all were treated with SP-nailing and no comparison to IP-nailing was made. It is noteworthy, however, that the absolute differences were small (reported SMD's ranged from -1.7 to 0.6 degrees) and therefore clinically irrelevant.⁸⁻¹⁰ Moreover, radiographs were used to measure alignment, whereas CTscans are superior in detecting malalignment. 13,38,39 The included studies in this review did not report on rotational malalignment based on CT-measurements. Low-dose CTbased data on rotational malalignment after SP-nailing is lacking and may be of added value to the ongoing debate on SP- or IP-nailing of tibial fractures as incidences up to 35% were reported after the IP-approach.^{38,39}

Finally, this review illustrates that the SP-approach does not substantially decrease the complication rate in comparison to the traditional IP-approach in nonunion, subsequent surgeries and impaired ROM.

Does the SP- Versus IP-Approach Affect Physical Functioning and Quality of Life?

There is little evidence whether the SP-approach leads to superior physical functioning and QoL in comparison with the IP-approach. MacDonald et al⁴³ reported a significant difference between SP and IP-nailing using Lysholm scores after 12 months with an excellent score for the SP-group and good score for the IP-group (93 vs. 84). Overall, the recovery of physical functioning and QoL following SP and IP-nailing seems good. Although, 9 different outcome measures were used making is difficult to compare study results.

Strengths and Limitations

This systematic review contains strengths and limitations. This is the first review that encompassed the complete spectrum of outcome measures, including pain, complications, physical functioning, and general QoL after SP and IPnailing. Second, search criteria were not limited by study design (eg, cohort study, RCT's), which provides a complete overview of all outcomes of interest published over the last decade. Third, this study provides a clinically question-driven overview about the ongoing debate on the nailing technique of tibial fractures.

Because of heterogeneity, inconsistent time-points, and a varying range of methodological quality, a pooled-analysis was not possible. However, results presented in this study were not subjected to any form of heterogeneity, and therefore validated and statistically reliable.

CONCLUSIONS

The SP and IP approach are both good techniques in tibial nailing with comparable results in anterior knee pain, complication rates (including retropatellar chondropathy, infection, and malalignment), physical functioning, and general QoL. The definitive choice should depend on the surgeon's experience and available resources.

ACKNOWLEDGMENTS

Mrs D.G. van Ittersum, medical librarian, for constructing the search strategy.

REFERENCES

- Tornetta P III, Collins E. Semiextended position of intramedullary nailing of the proximal tibia. Clin Orthop Relat Res. 1996:185–189.
- Tornetta P III, Riina J, Geller J, et al. Intraarticular anatomic risks of tibial nailing. J Orthop Trauma. 1999;13:247–251.
- 3. Cole JD. Distal tibia fracture: opinion: intramedullary nailing. *J Orthop Trauma*. 2006;20:73–74.
- Court-Brown CM, Gustilo T, Shaw AD. Knee pain after intramedullary tibial nailing: its incidence, etiology, and outcome. *J Orthop Trauma*. 1997:11:103–105.
- Katsoulis E, Court-Brown C, Giannoudis PV. Incidence and aetiology of anterior knee pain after intramedullary nailing of the femur and tibia. J Bone Joint Surg Br. 2006;88:576–580.
- Lefaivre KA, Guy P, Chan H, et al. Long-term follow-up of tibial shaft fractures treated with intramedullary nailing. *J Orthop Trauma*. 2008;22: 525–529
- Toivanen JA, Vaisto O, Kannus P, et al. Anterior knee pain after intramedullary nailing of fractures of the tibial shaft. A prospective, randomized study comparing two different nail-insertion techniques. *J Bone Joint Surg Am.* 2002;84:580–585.
- 8. Avilucea FR, Triantafillou K, Whiting PS, et al. Suprapatellar intramedullary nail technique lowers rate of malalignment of distal tibia fractures. *J Orthop Trauma*. 2016;30:557–560.
- Courtney PM, Boniello A, Donegan D, et al. Functional knee outcomes in infrapatellar and suprapatellar tibial nailing: does approach matter? *Am J Orthop.* 2015;44:E513–E516.
- Jones M, Parry M, Whitehouse M, et al. Radiologic outcome and patientreported function after intramedullary nailing: a comparison of the retropatellar and infrapatellar approach. J Orthop Trauma. 2014;28:256–262.
- Bible JE, Choxi AA, Dhulipala S, et al. Quantification of anterior cortical bone removal and intermeniscal ligament damage at the tibial nail entry zone using parapatellar and retropatellar approaches. *J Orthop Trauma*. 2013;27:437–441.

- Chan DS, Serrano-Riera R, Griffing R, et al. Suprapatellar versus infrapatellar tibial nail insertion: a prospective randomized control pilot study. *J Orthop Trauma*. 2016;30:130–134.
- Gelbke MK, Coombs D, Powell S, et al. Suprapatellar versus infrapatellar intramedullary nail insertion of the tibia: a cadaveric model for comparison of patellofemoral contact pressures and forces. *J Orthop Trauma*. 2010;24:665–671.
- Sanders RW, DiPasquale TG, Jordan CJ, et al. Semiextended intramedullary nailing of the tibia using a suprapatellar approach: radiographic results and clinical outcomes at a minimum of 12 months follow-up. J Orthop Trauma. 2014;28:245–255.
- Zamora R, Wright C, Short A, et al. Comparison between suprapatellar and parapatellar approaches for intramedullary nailing of the tibia. Cadaveric Study Inj. 2016;47:2087–2090.
- Marecek GS, Nicholson LT, Broghammer FH, et al. Risk of knee sepsis after treatment of open tibia fractures: a multicenter comparison of suprapatellar and infrapatellar approaches. J Orthop Trauma. 2018;32:88–92.
- Mitchell PM, Weisenthal BM, Collinge CA. No incidence of postoperative knee sepsis with suprapatellar nailing of open tibia fractures. J Orthop Trauma. 2017;31:85–89.
- Chen X, Xu HT, Zhang HJ, et al. Suprapatellar versus infrapatellar intramedullary nailing for treatment of tibial shaft fractures in adults. *Med Baltim.* 2018;97:e11799.
- Gao Z, Han W, Jia H. Suprapatellar versus infrapatellar intramedullary nailing for tibal shaft fractures: a meta-analysis of randomized controlled trials. *Med Baltim.* 2018;97:e10917.
- Ibrahim I, Johnson A, Rodriguez EK. Improved outcomes with semiextended nailing of tibial fractures? A systematic review. *J Orthop Trauma*. 2019;33:155–160.
- Wang C, Chen E, Ye C, et al. Suprapatellar versus infrapatellar approach for tibia intramedullary nailing: a meta-analysis. Int J Surg. 2018;51:133–139.
- Yang L, Sun Y, Li G. Comparison of suprapatellar and infrapatellar intramedullary nailing for tibial shaft fractures: a systematic review and meta-analysis. J Orthop Surg Res. 2018;13:146.
- Cazzato G, Saccomanno MF, Noia G, et al. Intramedullary nailing of tibial shaft fractures in the semi-extended position using a suprapatellar approach: a retrospective case series. *Injury*. 2018;49(suppl 3):S61–S64.
- Fu B. Locked META intramedullary nailing fixation for tibial fractures via a suprapatellar approach. *Indian J Orthop.* 2016;50:283–289.
- MacDonald DRW, Rehman H, Carnegie CA, et al. The Aberdeen weight-bearing test (knee): a new objective test for anterior knee discomfort. Eur J Trauma Emerg Surg. 2020;46:93–98.
- Sun Q, Nie X, Gong J, et al. The outcome comparison of the suprapatellar approach and infrapatellar approach for tibia intramedullary nailing. Int Orthop. 2016;40:2611–2617.
- Ozcan C, Turkmen I, Sokucu S. Comparison of three different approaches for anterior knee pain after tibia intramedullary nailing. Eur J Trauma Emerg Surg. 2020;46:99–105.
- Isaac M, O'Toole RV, Udogwu U, et al. Incidence of knee pain beyond 1 Year: suprapatellar versus infrapatellar approach for intramedullary nailing of the tibia. J Orthop Trauma. 2019;33:438–442.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.

- 30. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5:210.
- Law M, Stewart D, Pollock N, et al. Guidelines for critical review formquantitative studies. *Quant Rev Form Guidelines*. 1998.
- Meinberg EG, Agel J, Roberts CS, et al. Fracture and dislocation classification compendium-2018. *J Orthop Trauma*. 2018;32(suppl 1):S1–S170.
- Ryan SP, Steen B, Tornetta P III. Semi-extended nailing of metaphyseal tibia fractures: alignment and incidence of postoperative knee pain. J Orthop Trauma. 2014;28:263–269.
- Hessmann MH, Buhl M, Finkemeier C, et al. Suprapatellar nailing of fractures of the tibia. Oper Orthop Traumatol. 2020.
- Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Centers for disease control and prevention (CDC) hospital infection control practices advisory committee. Am J Infect Control. 1999;27:97–132; quiz 133-134; discussion 196.
- Milner SA. A more accurate method of measurement of angulation after fractures of the tibia. J Bone Joint Surg Br. 1997;79:972–974.
- Vallier HA, Cureton BA, Patterson BM. Randomized, prospective comparison of plate versus intramedullary nail fixation for distal tibia shaft fractures. J Orthop Trauma. 2011;25:736–741.
- Bleeker NJ, Cain M, Rego M, et al. Bilateral low-dose computed tomography assessment for post-operative rotational malalignment after intramedullary nailing for tibial shaft fractures: reliability of a practical imaging technique. *Injury*. 2018;49:1895–1900.
- Cain ME, Hendrickx LAM, Bleeker NJ, et al. Prevalence of rotational malalignment after intramedullary nailing of tibial shaft fractures: can we reliably use the contralateral uninjured side as the reference standard? J Bone Joint Surg Am. 2020;102:582–591.
- Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
- Cui Y, Hua X, Schmidutz F, et al. Suprapatellar versus infrapatellar approaches in the treatment of tibia intramedullary nailing: a retrospective cohort study. BMC Musculoskelet Disord. 2019;20:573.
- Leliveld MS, Verhofstad MH. Injury to the infrapatellar branch of the saphenous nerve, a possible cause for anterior knee pain after tibial nailing? *Injury*. 2012;43:779–783.
- MacDonald DRW, Caba-Doussoux P, Carnegie CA, et al. Tibial nailing using a suprapatellar rather than an infrapatellar approach significantly reduces anterior knee pain postoperatively: a multicentre clinical trial. *Bone Joint J.* 2019;101-B:1138–1143.
- 44. Weninger P, Schultz A, Traxler H, et al. Anatomical assessment of the Hoffa fat pad during insertion of a tibial intramedullary nail comparison of three surgical approaches. *J Trauma*. 2009;66:1140– 1145
- Chen CY, Lin KC, Yang SW, et al. Influence of nail prominence and insertion point on anterior knee pain after tibial intramedullary nailing. *Orthopedics*. 2014;37:e221–225.
- Boerger TO, Patel G, Murphy JP. Is routine removal of intramedullary nails justified. *Injury*. 1999;30:79–81.
- Eastman JG, Tseng SS, Lee MA, et al. The retropatellar portal as an alternative site for tibial nail insertion: a cadaveric study. *J Orthop Trauma*. 2010;24:659–664.