Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday, 04 May, 2023
1800 HOURS

LOCATION:
The River Mill Restaurant
2 Cataraqui Street, Kingston, ON
K7K 1Z6

PRESENTING ARTICLES:
Dr. Glenio Mizubuti & Dr. Devin Stirling

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

Supra-inguinal injection for fascia iliaca compartment block results in more consistent spread towards the lumbar plexus than an infra-inguinal injection: a volunteer study

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ABSTRACT

Background and objectives Lumbar plexus block has been used to provide postoperative analgesia after lower limb surgery. The fascia iliaca compartment block (FICB) has been proposed as an anterior approach of the lumbar plexus targeting the femoral, obturator and lateral femoral cutaneous nerve. However, both radiological and clinical evidence demonstrated that an infra-inguinal approach to the fascia iliaca compartment does not reliably block the three target nerves.
We hypothesized that a supra-inguinal approach of the fascia iliaca compartment results in a more consistent block of the three target nerves than an infra-inguinal approach.

Methods We performed a randomized controlled, double-blind trial in 10 healthy volunteers. Both an infra-inguinal FICB (I-FICB) and a supra-inguinal FICB (S-FICB) were performed on the left or the right side in each volunteer. Forty milliliters of lidocaine 0.5% was injected with each approach. Sensory and motor block and spread of local anesthetics (LA) on MRI were assessed.

Results After an S-FICB, 80% of the volunteers had a complete sensory block of the medial, anterior and lateral region of the thigh, compared with 30% after an I-FICB (p=0.035). There was an insignificant effect on motor function with both approaches. After an S-FICB, in 8 out of 10 volunteers there was spread of LA in the expected anatomic location of the obturator nerve on MRI compared with 1 out of 10 volunteers after an I-FICB (p=0.0017). The cranial spread of LA after an S-FICB on MRI was higher than after an I-FICB (p=0.007), whereas there was a more caudal spread of LA on MRI after an I-FICB than after an S-FICB (p=0.005).

Conclusions An S-FICB produces a more complete sensory block of the medial, anterior and lateral region of the thigh, compared with an I-FICB. Our study demonstrates that an S-FICB with 40 mL of LA more reliably spreads LA to the anatomical location of the three target nerves of the lumbar plexus on MRI than an I-FICB. An S-FICB also leads to a more consistent spread in a cranial direction under the fascia iliaca and around the psoas muscle.

Clinical trial registration This work was registered with the European clinical trial registry: Identifier Eudra CT 2015-004607-24.

INTRODUCTION

Different techniques for lumbar plexus blockade have been described providing postoperative analgesia after hip surgery.[1–3] Posterior approaches to the lumbar plexus are associated with complications, such as spinal and epidural anesthesia, nerve injury, risk of local anesthetic systemic toxicity (LAST) and retroperitoneal hemorrhage.[4] Moreover, posterior approaches to the lumbar plexus require the lateral or sitting position, which may be uncomfortable for patients with a hip fracture. Therefore, an anterior approach of the lumbar plexus, like the fascia iliaca compartment block (FICB), which can be performed in the supine position and has minimal associated risk, may be advantageous.

The fascia iliaca (FI) is the connective tissue layer that covers the anterior surface of the iliacus and psoas muscles. The FI is attached to the inner aspect of the iliac crest and blends medially with the psoas fascia, which surrounds the psoas muscle. The virtual space between the FI and the iliac muscle (IM) and psoas muscle (PM) forms the FI compartment (FIC). Therefore, it is theoretically possible to block the femoral nerve (FN), the obturator nerve (ON), and lateral femoral cutaneous nerve (LFCN) by a single injection into the FIC. Studies to date, however, suggest that an infra-inguinal injection of LA under the FI (I-FICB) does not reliably block these nerves.[5 6] Moreover, in at least one study, an I-FICB failed to provide adequate analgesia and did not decrease opioid consumption in patients after total hip arthroplasty.[5] Marhofer *et al* evaluated the spread of local anesthetics (LA) after an I-FICB using sensory block (pinprick) and MRI and concluded that the ON could not be blocked.[7]

To improve the spread of LA and the success of FICB's, Hebbard *et al* described a 'longitudinal supra-inguinal approach' (S-FICB), where LA is injected cranial to the inguinal ligament (IL).[8] In a cadaver study, Hebbard observed staining of FN and LFCN after injection of 20 mL of dye. A limitation of Hebbard's study is that he did not examine the ON.[8] A recent clinical study demonstrated that an S-FICB with a larger volume (40 mL of LA) resulted in a significant reduction of morphine consumption after total hip arthroplasty.[1]

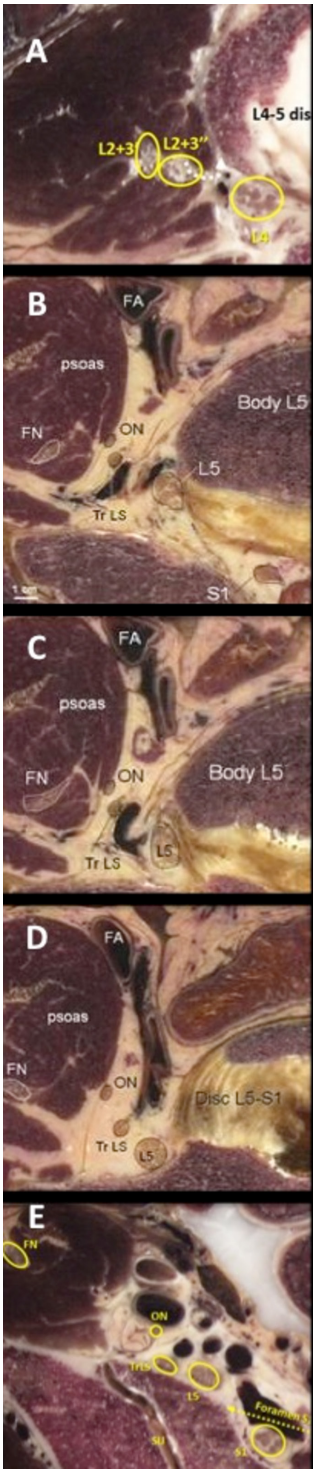

Figure 1 High-resolution axial cross-sections of the FIC of different axial levels between vertebrae L4 and S1. (A) At the level of the intervertebral disc of L4 and L5. L2+L3′ and the L4 nerves form the FN. L2+L3″ form the ON which then moves medially of the PM. (B) At the level of the vertebral body of L5 in close proximity of the TrLs. (C–E) FN travels further in the PM. (B–E) Femoral artery moves from the anterior part of the PM to the medial part and joins the ON, TrLs and the root L5. The ON descends medially to the PM and at first parallel to the TrLS. (E) At the level where the PM is joined by IM, the FN is clearly separated from the ON by a 'muscular bridge'. This is about the level of the intervertebral disc of L5–S1 up to the upper part of vertebral body of S1. At this level, the ON is no longer contained in the FIC. (Courtesy of Professor Gerbrand J Groen, Anesthesiology Pain Centre, University Medical Centre Groningen, University of Groningen, Netherlands; g.j.groen@umcg.nl.) Used with permission. FIC, fascia iliaca compartment; FN, femoral nerve; IM, iliac muscle; ON, obturator nerve; PM, psoas muscle; TrLs, lumbosacral trunk.

Anatomical considerations of the lumbar plexus and the FI

The lumbar plexus is formed from the ventral rami of the first four lumbar spinal nerves (L1–L4) with a contribution of the subcostal nerve. The FN, ON, and LFCN arise from these ventral rami within the PM. Figure 1 shows the origin of the three nerves within the PM (figure 1). The ventral branches of these ventral rami give rise to the FN and LFCN, and the dorsal branches give rise to the ON. The FN, ON and LFCN are

branches of the lumbar plexus that contribute to the innervation of the hip and of the lower limb. The lumbar plexus typically lies between the posterior mass of the PM (which is attached to the lumbar transverse processes) and the anterior mass of the PM (which is attached to the lips of the lumbar vertebral bodies, intervertebral discs and tendinous arches).[9] In a minority of the cases, the lumbar plexus lies entirely posterior of the PM.[9 10] After formation within the PM, the FN, ON and LFCN exit the PM at various levels. The LFCN and the FN leave at the level of vertebral body of L4 and L5, respectively, lateral to the PM. After its origin in the medial part of the PM, the ON descends medially to the PM (together with the iliaca vessels) and at first parallel to the lumbosacral trunk (TrLS). At the level where the PM is joined by IM, the FN is clearly separated from the ON by a 'muscular bridge' (figure 1). This is about the level of the L5–S1 disc.[3 11] At the body of the S1, the ON penetrates the fascia and is no longer part from the FI compartment. It then passes behind the common iliac artery and runs along the lateral wall of the lower pelvis to the upper part of the obturator foramen.[9 10]

Thus, the lumbar plexus is more or less 'in line' with the intervertebral foramina.[12] Within the psoas major ventral branches contribute to the FN and LFCN, whereas dorsal branches form the ON.[3 12]

From its exit lateral from the PM, the FN passes down between the PM and the IM, deep in the FI. The FN then travels posterior to the inguinal ligament (IL). The LFCN emerges from the lateral border of the PM at about its middle, and crosses anterior to the IM, deep to the FI, toward the anterior superior iliac spine (ASIS). It then passes underneath the IL. Both the FN and LFCN are contained within the FIC.

This study is a randomized controlled double-blinded trial, designed to test the hypothesis that an S-FICB more reliably reaches the anatomical position of three target nerves on MRI than an I-FICB. This study also hypothesized superior block characteristics of the three target nerves with an S-FICB.

METHODS

Study population, randomization and block approaches

After approval, 10 healthy volunteers were screened and recruited after obtaining written informed consent.

Exclusion criteria were age <18 years, body mass index >35, bodyweight <60 kg, allergy to LA, a history of liver or renal insufficiency, coagulopathy, clinical evidence of peripheral neuropathies, cardiac or pulmonary disease, abnormalities of sensory or motor function of the FN, ON or LFCN.

Before and after the performance of the FICB, sensory and motor block was evaluated and an MRI was performed. Using sealed, opaque envelopes, 10 volunteers were randomized. All volunteers received both approaches of the FICB, one approach on the right side and the other approach on the left side. Randomization determined which approach (S-FICB or I-FICB) was performed on the right side. As such, every volunteer acted as his or her own control.

All volunteers were monitored with non-invasive blood pressure measurements, oxygen saturation and ECG throughout the study. Resuscitation medication and equipment was available.

All FICB's were performed with ultrasound (US) (Flex Focus 400, 18–6 MHz linear array probe; BK Ultrasound, Peabody, Massachusetts, USA) and a 22-gage, 8 cm needle (Sonoplex Stim cannula, Pajunk Medizintechnologie, Geisingen, Germany). The FICB on the right side was performed first in each patient with the approach according to randomization. Forty millilitres of lidocaine 0.5% (lidocaine hydrochloride monohydrate, B. Braun Medical, Oss, the Netherlands) was injected incrementally after intermittent negative aspiration on each side. In total, 80 mL (40 mL per approach) of lidocaine 0.5% was injected per volunteer.

Two experienced anaesthesiologists (KV and IL) performed all FICB's. One anaesthesiologist performed all I-FICBs, the other performed all the S-FICBs; for both anaesthesiologists the block they performed was their preferred approach to the FIC. Both were present during performance and agreed on the adequacy of needle placement and spread of LA during injection of every injection performed.

Infra-inguinal transverse FICB

As described by Shariat,[5] the US transducer was placed caudal to the IL in the inguinal crease with a transverse orientation. The ultrasound landmarks were identified: IM, sartorius muscle (SM), FI, FN, and the femoral artery and vein. The transducer was moved laterally along the FI toward the crossing with the medial boarder of the SM. The needle was advanced in plane from lateral to medial and pierced the FI at the intersection of the IM and medial border of the SM in the inguinal crease. Repositioning of the needle was allowed to achieve 'adequate' spread with the 40 mL of LA. Correct injection resulted in separation of the FI and the IM in the medial–lateral direction from the point of injection. An injection was considered successful when the spread of LA on US reached the FN medially and at least 3 cm laterally from the point of injection beneath the FI.[4]

Supra-inguinal longitudinal FICB (S-FICB)

The US transducer was positioned longitudinally at the level of the ASIS as described in the study of Desmet *et al*.[1] By sliding the US transducer in a medial and caudal direction, the IM and FI were identified. To obtain a 'bow-tie sign' the transducer was rotated slightly so that the cranial end of the transducer points to the umbilicus and the caudal end pointed at the ASIS. This way the transducer is positioned in the parasagittal plane and the deep circumflex iliac artery (DCIA) was identified, which is an important US landmark. The DCIA arises from the external iliac artery and runs approximately 1 cm cranial of the IL in a fibrous sheath formed by the transversalis fascia and FI. It is a good US-guided reference for the S-FICB and was seen in all volunteers. The needle was introduced in plane from caudal to cranial under US guidance until the tip of the needle was positioned under the FI at the level of the DCIA. Injection with 40 mL of LA was considered successful if hydrodissection between the FI and the IM occurred and if cranial spread of LA under the FI was present. Repositioning of the needle was allowed during the injection to achieve 'adequate' spread.

Nerve block assessment

The following tests were used to assess the block of the FN, ON, and LFCN: sensory and motor block in the different nerve territories and the spread of LA on MRI in the coronal and axial plane.

Block characteristics

Sensory block testing

The sensory block was assessed with ice cube. A blinded investigator evaluated cold sensation of the thigh at two time points: before (t0) and 1 hour (t1) after the performance of FICB.[5 13–15] Sensation to cold was scored using a categorical scale from 0 to 2 (0=absence of cold sensation, 1=diminished cold sensation and 2=normal sensation) and compared with the upper arm. A

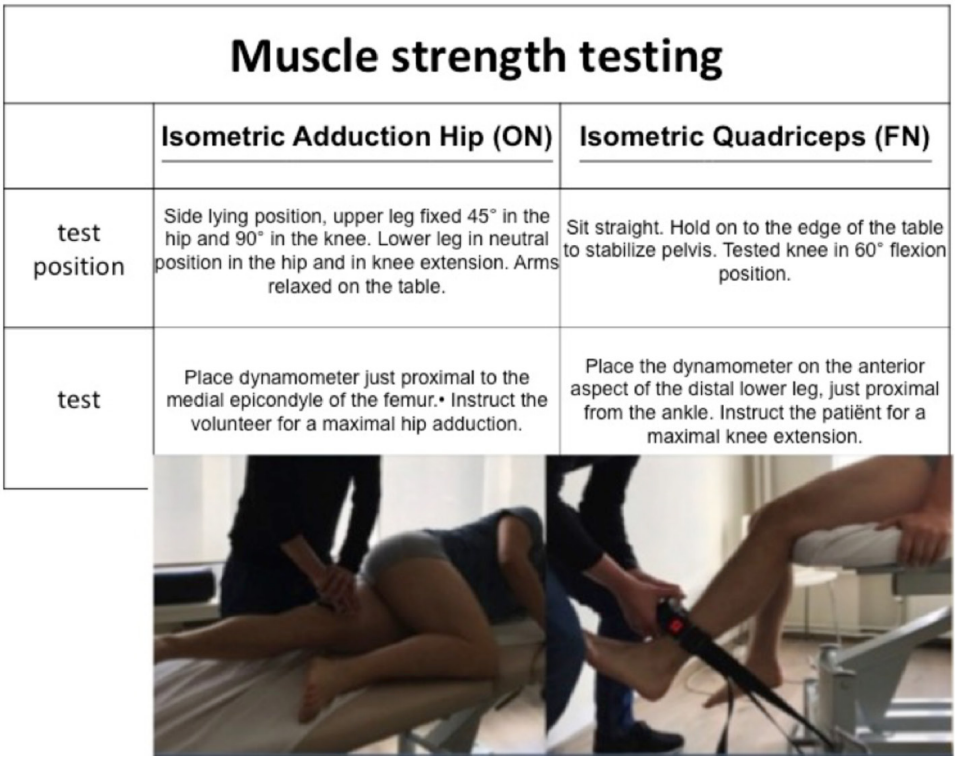

Figure 2 Description of the muscle strength testing with the dynamometer (MicroFET2) for the different muscle groups.

'complete block' was defined as absence of cold sensation on the anterior, medial and lateral aspect of the thigh.

To evaluate a clinical block of the FN and LFCN, a sensory assessment of the anterior and lateral part of the thigh is adequate. Sensation on the medial part of the thigh was tested although, according to literature the medial part of the thigh is not consistently innervated by the ON.[16]

Muscle strength testing

Motor block was evaluated using a dynamometer (MicroFET2; Procare, Groningen, the Netherlands) (figure 2).[17 18] Muscle strength was assessed in Newton. Muscle strength test was performed at the following time points: before (T0) and 1 and 2 hours (T1 and T2, respectively) after performance of the FICB. All testing was performed by a blinded, physiotherapist specialized in revalidation and trained in the use of a dynamometer.[11] The technique to test the adductor muscles (innervated by the ON) and quadriceps muscles (innervated by FN) is as described and depicted in figure 2.

MRI

Pelvis, hip, and groin region were scanned (from the cranial part of the kidney to 2 cm caudal of the lesser trochanter of the femur) with axial and coronal T1 and T2 Ideal (with/without fat-suppression) MRI (1.5T HDXT; GE Healthcare, Chicago, Illinois, USA) sequences. The craniocaudal spread (in the coronal plane) of LA and the spread of LA around the PM (in the axial plane) were determined. Special attention was paid at the suggested anatomical locations of the three nerves (FN, ON and the LFCN) as previously described in the Introduction section (figure 1).

At present. there is no standardized method described to objectively evaluate spread of LA after FICB. We therefore developed a measurement system to objectively describe spread of LA.

Evaluation of the spread of the LA in the coronal plane

To evaluate the craniocaudal spread, we defined the reference line as the line between both ASIS (figure 3). A radiologist, unaware of the randomization process, evaluated the craniocaudal spread of LA in the coronal plane starting 20 mm cranial and ending 300 mm caudal from this reference line (figure 3). The zero-reference line corresponds with the intervertebral disc of L4 and L5, which is the level where the FN and ON are formed (figure 1). An overview of the most important cross-sections in relation to the lumbar vertebrae is described in table 1. As such, the craniocaudal extension of the spread of LA of both techniques could be compared (figure 1, table 1).

Evaluation of the spread of the LA in the axial plane

Seventeen axial MRI images, starting 20 mm cranial and ending 300 mm caudal to the reference line with 10 mm intervals, were evaluated in every subject to determine the spread of LA in the axial plane. To quantify the spread of LA, a 12-sector radar chart was centered over the PM bilaterally. The axial spread of LA was assessed around the PM for both approaches left and right. For each of the 12 sectors (of that level) of the radar chart, the spread of LA was scored with 0 (no LA present) or 1 (LA present) by the radiologist. This score was compared bilaterally (figure 4).

For each nerve, the anatomical location (territory in which the FN, ON, and LFCN are located) in relation to the PM was determined to quantify and evaluate the spread.[3] For the ON, the levels between the reference line and −60 mm are the most relevant due to the suggested anatomical position of the ON. For the FN and the LFCN, all levels downwards the reference line are relevant up until −100 mm (caudal) the reference line (figures 1 and 4) (table 1).

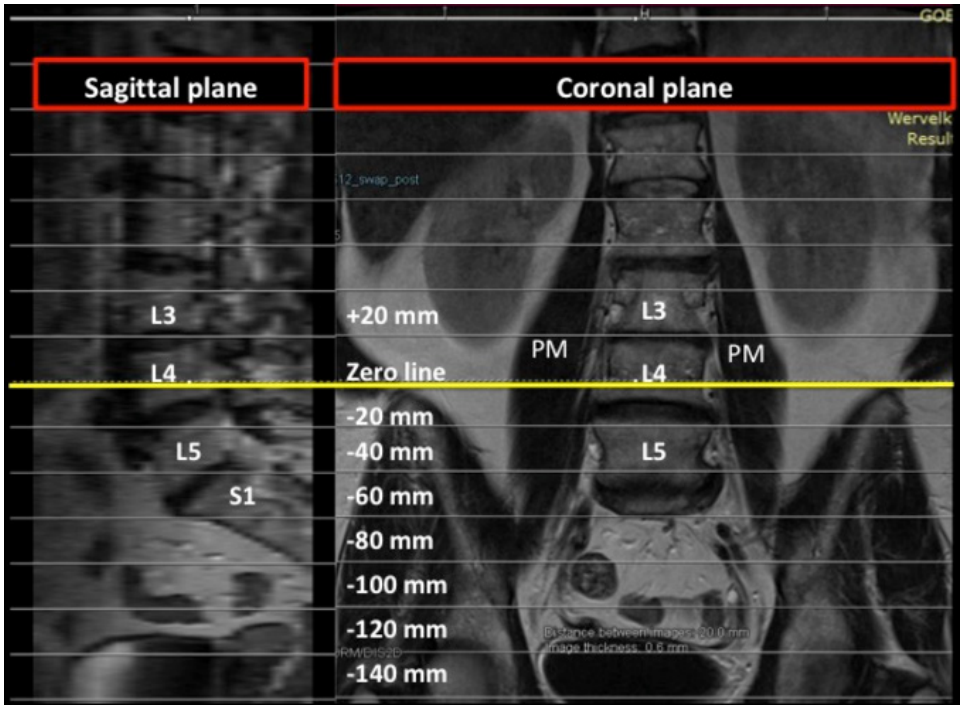

Figure 3 Sagittal and coronal MRI with zero line (yellow line) in correlation with lumbar vertebral column. The zero-reference line is the line connecting both anterior superior iliac spines. PM, psoas muscle.

Data analysis and statistics

The primary outcome parameter was the presence of a sensory block in the three target nerves (lateral, medial and anterior thigh). Based on previous publications, an incidence of a sensory block in the three target nerves of 12.5% after an I-FICB and 67% after S-FICB was used for sample size calculation. To obtain a power of 80% with an α of 0.05 (Z-test with pooled variance), 10 volunteers were needed.[14] Data regarding sensory block were presented as proportions and analyzed using the Fisher's exact test.

Secondary outcome parameter was the spread of LA on MRI. Data analysis was performed using χ^2 tests to compare the spread of LA in the axial plane and the Wilcoxon matched pairs tests for the comparison in the coronal plane. Data were presented as median (range) or proportions were appropriate.

RESULTS

Volunteers were 19 or 20 years old (six females/4 men) with an average weight of 72 kg (65–83 kg). According to the procedure described in the Method section, needle positioning and spread of LA was considered adequate for all blocks. No adverse events were noted during and after the study period.

Table 1 Correlation between the axial slices on MRI and anatomical landmarks

Level on axial MRI	Anatomical landmark
+20 mm to 0	Vertebral body of L4
0 to –20 mm	Intervertebral disc of L4 and L5
–20 mm to –40 mm	Vertebral body of L5
–40 mm to –60 mm	Intervertebral body of L5 and S1
–60 mm to –80 mm	Vertebral body of S2 and S3
–80 mm to –100 mm	Roof of the acetabulum
–100 mm to –120 mm	Femoral head

0=reference line: line connecting both anterior superior iliac spines.

Block characteristics

Sensory testing

Before the performance of the FICB, all subjects had normal sensation to cold in both limbs.

After an S-FICB, 80% of the volunteers had a complete sensory block of the three regions of the thigh, compared with 30% after the I-FICB (p=0.035) at T1 (table 2).

Muscle strength testing

Muscle strength measurements were similar for both limbs before performance of the FICBs. The decrease of motor strength in both groups after the FICB was clinically and statistically insignificant.

MRI

Spread of LA in the coronal plane

In the coronal plane, cranial spread of LA after an S-FICB was higher than after an I-FICB (median+1 mm (cranial) to the reference line (range −5 mm to +28 mm) vs −18.5 mm (caudal) to the reference line (range −70 mm to 0 mm) (p=0.007)). Caudal spread of LA after an I-FICB was lower than after an S-FICB (median −225 mm (caudal) to the reference line (range −242 mm to −200 mm) vs median of −171 mm (caudal) to the reference line (range −193 mm to −151 mm (p=0.005)) (figures 3 and 5).

Spread of the LA in the axial plane

In total, 4080 sectors were evaluated (10 volunteers×2 (bilateral)×17 (axial levels)×12 sectors). Scores per level for the different approaches were compared.

In general, there was a more extensive spread (more volunteers where LA could be traced in the anatomical location of the nerves) after an S-FICB in comparison with an I-FICB in the range between +20 mm above the reference line up until −80 mm from the reference line (table 3) (figure 6).

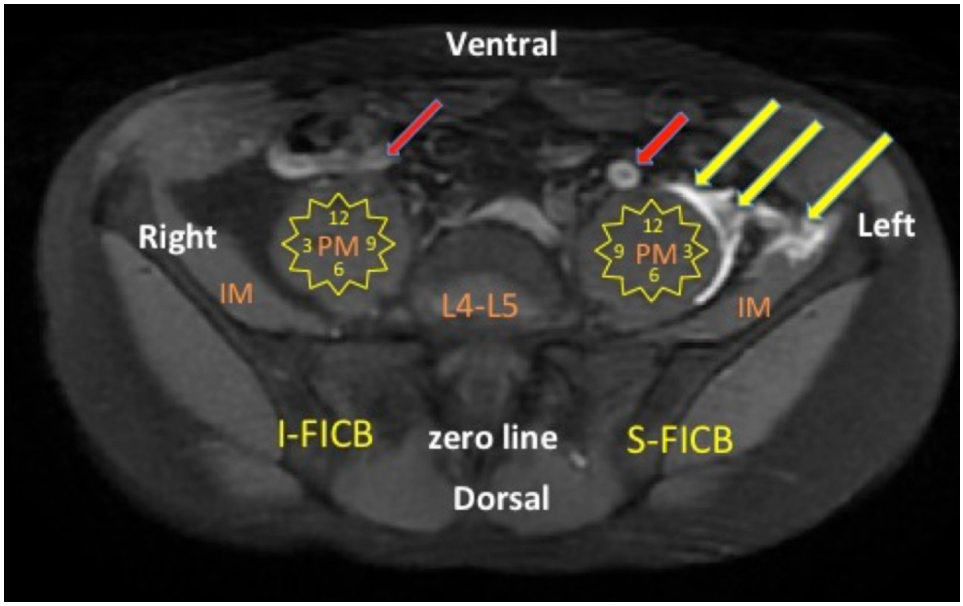

Figure 4 Method to evaluate axial spread of the LA (axial view at the reference line as example image corresponding with lower part of the body of L4 and the L4–L5 interspace). 12 sector raster: yellow raster counter clockwise on the right PM, clockwise on the left PM. Yellow arrows indicate LA and red arrows indicate iliac artery. IM, iliac muscle; LA, local anesthetics; PM, psoas muscle.

Looking at the anatomical locations of the different nerves LA was statistically more present after an S-FICB (9/10) than after an I-FICB (1/10) (p=0.0011) for the ON anatomical relevant sectors. Highest presence of LA (most relevant sectors positive for LA presence) at the anatomically suggested position of the ON was seen between −40 and −60 mm corresponding with the bottom plate of L5 and the body of S1 (table 3).

For the FN and the LFCN, there was no significant difference between the two approaches (table 3).

DISCUSSION

Our study demonstrates that an S-FICB more reliably blocks the medial, anterior and lateral thigh than an I-FICB. In our study protocol, the primary endpoint of 'complete block' was defined as a block of the FN, ON and LFCN. To evaluate a clinical block of the FN and LFCN, a sensory assessment of the anterior and lateral part of the thigh is adequate. However, the sensory distribution of the ON is debatable. The medial part of the thigh is not consistently innervated by the ON, indeed in Bouaziz *et al*[16] described that in 57% of the patients the cutaneous contribution of the ON was absent. Therefore, only a significant reduction of adductor strength is the only reliable test for true ON blockade. It is important to point out that as the pectineal muscle is innervated by the FN, at least 75% reduction of muscle strength during adduction is necessary to confirm a block of the ON if, as is the case after a FICB, the FN is also blocked. This high percentage (75%) is necessary to distinguish between ON blockade and a possible adduction due to sciatic nerve innervation since the sciatic nerve also partially innervates the adductor muscles.

As our study protocol required simultaneous bilateral FICB's, the total dose of LA was limited to avoid LAST. As the FICB is a field block, a large volume of LA is necessary to achieve an adequate spread of the different target nerves. Therefore, we had to reduce the concentration of lidocaine to 0.5%. The results of the motor block were inconclusive. Due to the relatively weak motor block, we were not able to assess the effects of the S-FICB and I-FICB on the adductor muscles innervated by the ON.

We therefore determined the spread of LA with MRI in the anatomical location where the ON is attainable with a FICB as a surrogate for the clinical evaluation of an ON block. Our results demonstrate that in 80% of the volunteers, LA was present in the anatomical location of the ON after an S-FICB compared with 10% after an I-FICB.

The overall findings are consistent with the variable block success demonstrated by Shariat and colleagues[5] after an I-FICB and the higher success rate demonstrated by Desmet and colleagues[1] using an S-FICB.

The clinical results of the sensory block of the FN in the I-FICB group were unexpected since LA contacted the nerve in all volunteers, but sensory block of the thigh was inferior to the S-FICB group. This indicates that, whatever the reason, the I-FICB, at least with dilute LA, will not invariably lead to a consistent block of the FN. We can only hypothesize that a proximal piercing of the fascia lata by the anterior femoral cutaneous nerves could explain this unexpected low success rate. We are unaware of literature that might support our hypothesis; however, our results are very similar to the results of the study by Shariat *et al*.[5] Indeed, in their study, only 38% of the patients had evidence of a sensory nerve block of the FN with a similar I-FICB. This indicates that, whatever the reason, the I-FICB will not inevitably lead to a consistent FN block.

Table 2 Proportions of volunteers having 'no block', 'partial block' or full block" after 1 hour

	Anterior thigh		Medial thigh		Lateral thigh	
	S-FICB	I-FICB	S-FICB	I-FICB	S-FICB	I-FCIB
No sensory block	0/10	3/10	0/10	2/10	1/10	3/10
Partial sensory block	1/10	3/10	1/10	4/10	1/10	2/10
Full sensory block	9/10	4/10	9/10	4/10	8/10	5/10

I-FICB, infra-inguinal fascia iliaca compartment block; S-FICB, supra-inguinal fascia iliaca compartment block.

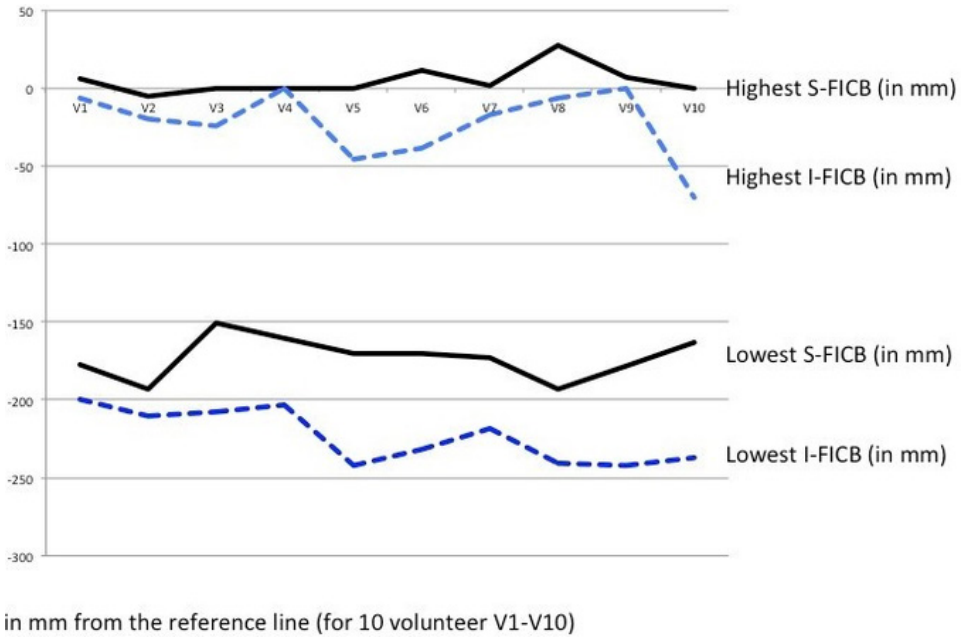

Figure 5 Results of the cranial and caudal spread of LA in the coronal plane for both approaches. Highest and lowest points for S-FICB (full lines) and I-FICB (dashed lines) for all volunteers (V1–V10). 0, reference line; I-FICB, infra-inguinal fascia iliaca compartment block; LA, local anesthetics; S-FICB, supra-inguinal fascia iliaca compartment block.

Limitations

First, while we clearly defined the ultrasound endpoints for correct needle positioning and injection, the fact that two researchers agreed on the correct injection during the blocks could potentially lead to bias in favor of one of the two approaches.

Second, as the results of the motor block evaluation were inconclusive, due to the low concentrations of LA used, we were unable to formally evaluate the effect of a FICB on the ON. We therefore relied on the presence of LA in the anatomical position of the ON. As this interpretation is based on anatomical landmarks and not on actual MRI visualization of the nerves we developed a scoring system that can be reproduced. As the nerve itself cannot be visualized, we could not account for anatomical variations that might influence the effect of a FICB in clinical practice. We are fully aware that this is only a surrogate for a clinical evaluation of ON blockade. Further research is necessary with consecutive FICB's in order to allow the use of larger doses of LA to effectively evaluate the clinical effect of the different approaches of the FICB.

Table 3 Number of volunteers with local anesthetics in the anatomical location of the different nerves at different levels

	FN and LFCN						ON					
		Number of sectors positive		Number of volunteers positive				Number of sectors positive		number of volunteers positive		
	SECTOR	S-FICB	I-FICB	S-FICB	I-FICB	P value	SECTOR	S-FICB	I-FICB	S-FICB	I-FICB	P value
Zero-reference line	12-1-2-3-4-5-6-7-8-9	26	3	6	3	NS	6-7-8-9-10-11-12-1	3	1	1	0	NS
–10 mm	12-1-2-3-4-5-6-7-8-9	34	8	7	5	NS	6-7-8-9-10-11-12-1	2	1	1	0	NS
–20 mm	12-1-2-3-4-5-6-7-8-9	41	12	8	5	NS	6-7-8-9-10-11-12-1	10	1	5	0	0.0325*
–30 mm	12-1-2-3-4-5-6-7-8-9	44	16	8	5	NS	6-7-8-9-10-11-12-1	14	5	5	0	0.0325*
–40 mm	12-1-2-3-4-5-6-7	44	23	9	6	NS	6-7-8-9-10-11-12	12	6	6	1	NS
–50 mm	11-12-1-2-3-4-5-6	43	23	7	6	NS	6-7-8-9-10-11-12-1	18	1	9	0	0.0001†
–60 mm	11-12-1-2-3-4-5-6	22	18	7	6	NS	6-7-8-9-10-11-12-1	8	2	8	1	0.0055†
–70 mm	1-2-3-4-5-6	16	13	7	7	NS	NR	NR	NR	NR	NR	
–80 mm	2-3-4-5-6	12	14	8	8	NS	NR	NR	NR	NR	NR	
–90 mm	2-3-4-5-6	10	11	8	8	NS	NR	NR	NR	NR	NR	
–100 mm	2-3-4-5-6	10	12	7	8	NS	NR	NR	NR	NR	NR	

Spread at different levels (from 20 mm above reference line up to –100 mm below the reference line) for the different nerves (ON, FN, LFCN).
S-FICB means more positive (LA covered) sectors of the grid per level.
*Non-significant after Bonferroni-Holmes correction for multiple comparisons.
†Significant after Bonferroni-Holmes correction for multiple comparisons.
FN, femoral nerve; I-FICB, infra-inguinal fascia iliaca compartment block; LFCN, lateral femoral cutaneous nerve; NR, non-relevant; NS, non-significant; ON, obturator nerve; S-FICB, supra-inguinal fascia iliaca compartment block.

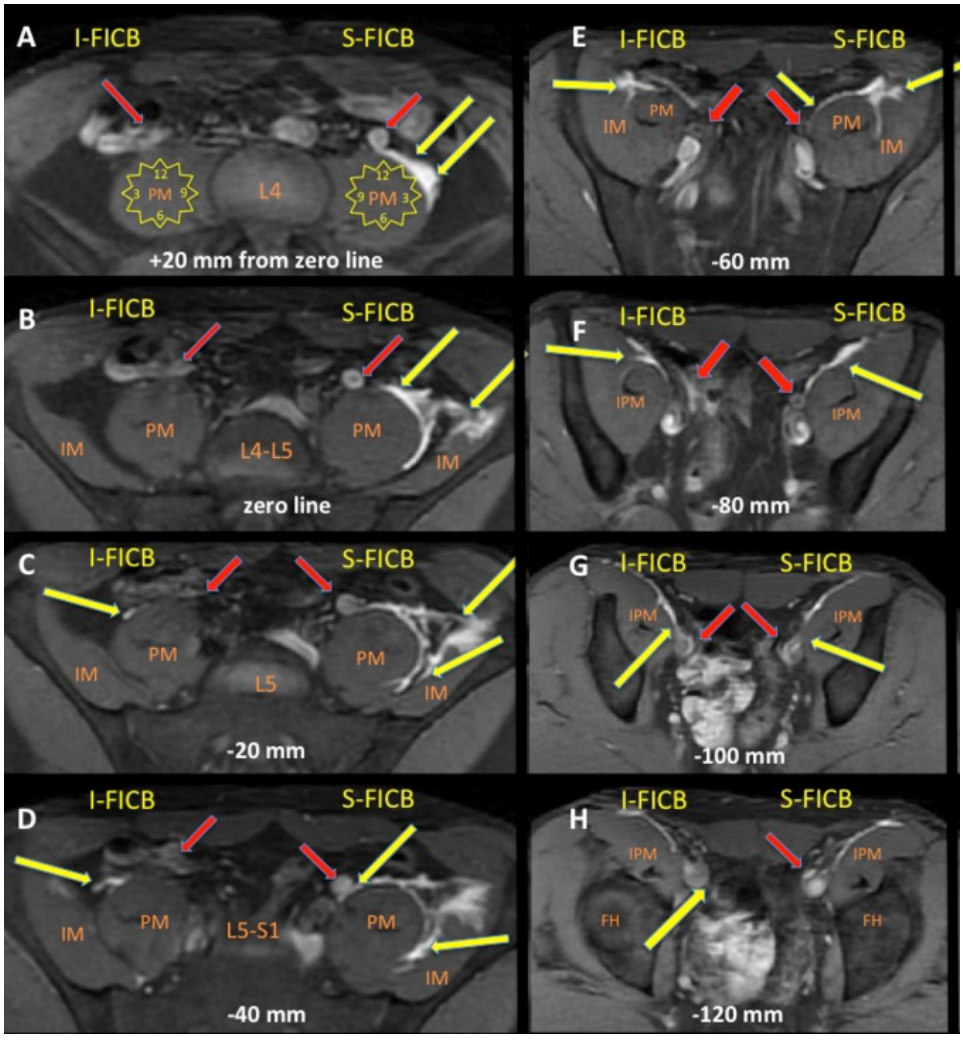

Figure 6 Spread of LA on axial MRI (T1 fat-sat) at different levels between A (+20 mm) to H (−100 mm) of the reference line (drawn between the two anterior superior iliac spines). FH, femoral head; I-FICB, infra-inguinal fascia iliaca compartment block; IM, Iliac muscle; IPM, iliopsoas muscle; LA, local anesthetics; PM, psoas muscle; S-FICB, supra-inguinal fascia iliaca compartment block. Yellow arrows indicate LA and red arrows indicate iliac artery.

Finally, we did not investigate the role of volume and concentration on the clinical effects of a FICB. The volume of 40 mL for each block was based on unpublished research in cadavers in which the spread of different volumes was studied. In clinical practice, early rehabilitation can be impeded by both insufficient analgesia or a clinically relevant motor block, so further research will need to focus on the ideal volume, concentration and type of LA for the FICB.

CONCLUSIONS

An S-FICB produces a more consistent sensory block of the medial, anterior and lateral thigh, compared with an I-FICB. Block of the ON was not proven, and although LA spread to the usual anatomic location of the ON was more consistently achieved with the S-FICB. The clinical impact of this spread remains to be shown. Our study demonstrates that an S-FICB with 40 mL of LA more reliably spreads LA in the anatomical location of the three target nerves of the lumbar plexus on MRI than an I-FICB. An S-FICB also leads to a more consistent spread in a cranial direction under the FI and around the PM. More research is required to evaluate the clinical effects of an S-FICB.

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Review article

The effect of regional nerve block on perioperative delirium in hip fracture surgery for the elderly: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: With minimal systemic toxicity, an analgesic effect of regional nerve block (RNB) has been proved in hip fracture cases. Analgesia was expected to reduce delirium by controlling pain, a known predisposing factor for delirium. We performed a meta-analysis to investigate the effect of RNB on delirium after hip fracture surgery in elderly patients. We aimed to answer the question: Can regional nerve block reduce postoperative delirium in hip fracture patients?
Hypothesis: Our hypothesis was that RNB could reduce postoperative delirium after hip fracture surgery in elderly patients.
Patients and Methods: MEDLINE, Embase, and Cochrane Library databases were searched systematically for studies published before September 9, 2020, investigating the effect of RNB on perioperative delirium after hip fracture in elderly patients. We performed synthetic analyses for overall RNB compared to a control group both in 1) overall elderly patients, including the cognitively impaired, and 2) for patients without cognitive impairment (CoI). Also, we performed subgroup analyses for each of the block techniques, such as fascia-iliac block (FIB) and femoral nerve block (FNB).
Results: Eight randomized controlled trials compared the incidence of perioperative delirium between the RNB and control groups. A pooled analysis showed no differences in delirium incidence between the RNB and control groups (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.36–1.22; $p = 0.18$; $I^2 = 58\%$) in overall elderly patients. However, there was a significant reduction of delirium in the RNB group in patients without CoI (OR: 0.44; 95% CI: 0.21–0.94; $p = 0.03$; $I^2 = 51\%$). In the subgroup analyses, we were unable to discern any differences in delirium incidence between the groups for FIB (OR, 0.89; 95% CI: 0.19–4.19; $p = 0.88$; $I^2 = 78\%$) and FNB (OR 0.61; 95% CI: 0.31–1.20, $p = 0.15$, $I^2 = 47\%$).
Conclusions: In cases of hip fracture in elderly, RNB demonstrated a preventive effect on perioperative delirium for patients without preoperative CoI. No significant reduction in perioperative delirium was observed when cognitively impaired patients were included.

1. Introduction

Elderly patients with hip fractures commonly have multiple comorbidities, and the perioperative mortality rate is known to increase by >10% after several complications [1,2]. Delirium is a major complication in elderly patients with hip fractures, of whom approximately 61% have delirium in the perioperative period [3]. Patients with delirium are also well known to less likely return to their preinjury function level [4]. Aging, preoperative cognitive disorder, psychiatric illness, decreased functional status, and severe postoperative pain are known risk factors that cause delirium [5]. Several previous studies reported on multimodal approaches as a part of the effort to prevent or enhance recovery from perioperative delirium after hip fracture surgery in the elderly [6,7]. A number of studies investigated the effect of perioperative pain management, a

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major controllable factor, to reduce the incidence of postoperative delirium after hip fracture [8,9].

Systemic analgesia, preoperative traction, transcutaneous electrical nerve stimulation, and nerve blocks have been investigated to control pain in hip fracture patients [10]. Enteral or parenteral opioids are mainstays of pain management, but care should be taken regarding the efficacy and side effects of these drugs considering the impaired metabolism, excretion, and physical reserve of elderly patients [11]. In addition, cognitive impairment (CoI) influences pain assessment, which relies on self-report, causing underdetection and undertreatment [12]. To overcome these problems, regional nerve blocks (RNB) such as the fascia iliaca block (FIB) and femoral nerve block (FNB) have emerged recently as attractive alternatives to systemic opioids in cases of hip fracture. With minimal systemic toxicity, the analgesic effect of RNB has been proved in hip fractures and is expected to reduce delirium by controlling pain, a predisposing factor for delirium [13].

Although many studies have reported the relationship between RNB and perioperative delirium in elderly hip fracture patients, to our best knowledge, no meta-analysis with a high level of evidence has been reported previously.

Meanwhile, previous studies have demonstrated an insufficient preventive effect of RNB on the occurrence of delirium in patients at high risk for perioperative delirium [8]. As CoI is one of the strongest preoperative risk factors, cognitively impaired patients are prone to develop delirium despite various preventive measures [3]. Therefore, we investigated the effectiveness of RNB, compared with usual care or other interventions, for reducing the development of delirium in elderly patients, including those with and without CoI.

We asked the following question: Can regional nerve block reduce postoperative delirium in hip fracture patients? Our hypothesis was that RNB could reduce delirium in the postoperative period after hip fracture surgery in elderly patients.

2. Materials and Methods

This study was performed in accordance with Cochrane Review and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines [14,15].

2.1. Literature search

Based on these guidelines, we searched the MEDLINE, Embase, and Cochrane Library databases for comparative studies investigating the effect of RNB on delirium incidence after hip fracture surgeries. The search was performed for articles from inception to September 7, 2020, using an a priori search strategy. Search terms included synonyms and related terms for hip fracture, RNB, and delirium as follows: ("Hip" OR "femur" OR "intertrochanter*" OR "pertrochanter*" OR "proximal femur") AND (fracture) AND ("nerve block" OR "Block*" OR "nerve analgesia" OR "analgesic") AND ("delirium" OR "cognitive disorder" OR "cognitive"). There were no restrictions on language, publication year, or type of publication. After the initial electronic search, relevant studies and their bibliographies also were manually searched. The individual search strategies are listed in the Supplementary electronic annexure.

2.2. Study selection

From the titles and abstracts of the studies, studies for full-text review were selected independently by two board-certified orthopedic surgeons with hip and pelvic trauma fellowships. If the abstract provided insufficient data to make a decision, the full article was reviewed.

The inclusion criteria were:

- the RCT of the original research articles;
- studies that directly compared perioperative (with the postoperative period investigated regardless of the preoperative period) delirium between the RNB and control groups and;
- studies conducted on proximal femoral fractures such as femoral neck and pertrochanteric fractures.

We excluded non-RCTs of original articles, biomechanical and cadaveric studies, technical notes, letters to the editor, expert opinions, review articles, meta-analyses, conference abstracts, and case reports. We also combined duplicate studies using the same patients that should have been published as one study.

At each stage of study selection, the κ-value was calculated to determine inter-reviewer agreement regarding study selection. Agreement between reviewers was correlated a priori with κ-values as follows: $\kappa = 1$, $1.0 > \kappa \geq 0.8$, $0.8 > \kappa \geq 0.6$, $0.6 > \kappa \geq 0.4$, $0.4 > \kappa \geq 0.2$, and $\kappa < 0.2$ corresponded to "perfect," "almost perfect," "substantial," "moderate," "fair," and "slight" agreement, respectively. Disagreements at each stage were resolved by consensus between the two investigators, or by discussion with a third investigator who was a board-certified orthopedic surgeon when the consensus could not be reached.

2.3. Data extraction

For qualitative synthesis, the following information and variables were extracted using a standardized form. The demographics of each study included study design, total number of patients, mean age, sex, fracture type investigated, surgical delay, cognitive status of patients, type of RNB and management in the control group, and delirium incidence. In addition, for the details of each study, the variables investigated were anesthesia for fracture surgeries, the RNB technique and dosage, RNB timing, count of the RNB, diagnostic tool for delirium, pain score, and other pain medications in both groups. For the meta-analysis, we extracted the data on delirium incidence from the included studies for the RNB and control groups. For data extraction, the same two board-certified orthopedic surgeons who participated in the study selection independently recorded the data from each enrolled study. Disagreements between the two reviewers were resolved by discussion between them.

2.4. Data synthesis and statistical analyses

The main outcome of our meta-analysis was a comparison of the incidence of postoperative delirium after hip fracture surgeries between the RNB and control groups. We performed synthetic analysis for overall RNB compared to the control group for: (1) all included patients, including the cognitively impaired. Then, additional synthetic analysis was performed to compare the RNB with the control group; (2) for patients without CoI. If there was no specific information on the incidence of delirium according to the presence or absence of CoI, the study was excluded from this analysis. Subgroup analysis was performed for each of the block techniques, such as FIB and FNB in all included patients.

For all comparisons, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as dichotomous data. Heterogeneity was assessed using the I^2 statistic, in which 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively. Forest plots were used to show the outcomes, pooled estimates of effects, and overall summary effect of each study. Statistical significance was set at $p < 0.05$. All data were pooled using a random-effects model, which was recommended previously to avoid overestimation of the study results, especially in the field of medicine [16]. We did not perform the test for publication bias because the evaluation typically is performed only when at least

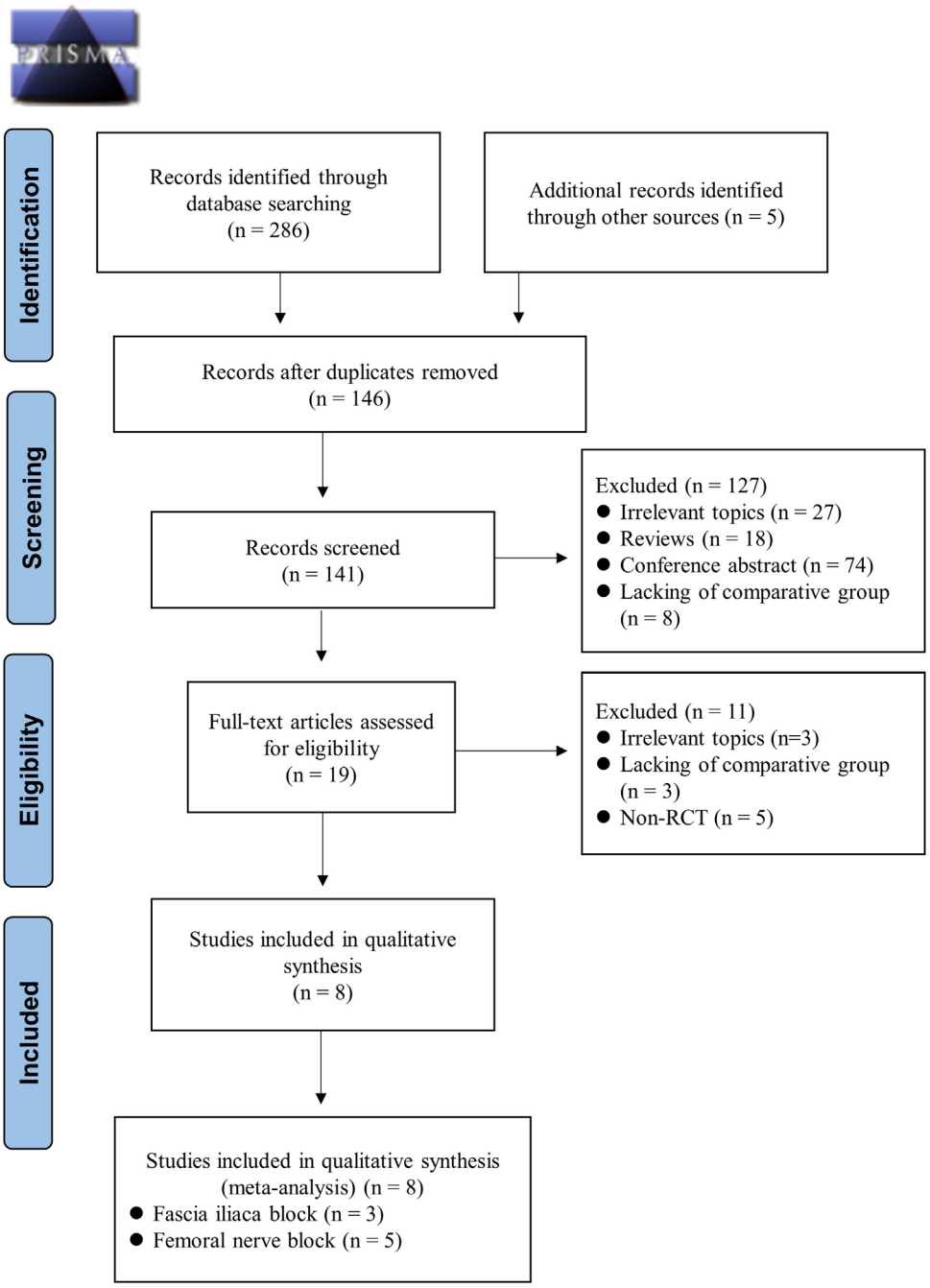

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of literature selection.

10 studies are included in the meta-analysis [17]. All statistical analyses were performed using Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; 2014).

3. Results

3.1. Study identification

The details of the study identification and selection process are summarized in Fig. 1. The initial electronic literature search yielded 286 articles, and manual searching five studies were added. After removing 146 duplicates, 141 studies were screened. Later, 127 studies were excluded after their titles and abstracts were reviewed; and an additional 11 studies were excluded after full-text review because 3 studies were not in the field of interest, 3 had insufficient data for comparative study, and 5 studies were non-RCTs. Accordingly, 8 studies were eligible for data extraction and meta-analysis. Agreement between the reviewers on study selection was "substantial" at the title review stage ($\kappa = 0.789$) and "almost perfect" at the abstract ($\kappa = 0.858$) and full-text ($\kappa = 0.881$) review stages.

3.2. Qualitative synthesis

3.2.1. Study characteristics and demographics

All 8 included studies were RCTs [8,9,18–23]. In total, 941 hip fracture cases were included in the selected studies, in which

Table 1
Study design and demographic data.

Author (year)	Study design	No. of patients		Mean age (years)	Female sex (%)	Fracture type	Mean surgical delay (hours)		Patients with cognitive impairment	Type of nerve block	Pain management in control group
		RNB	Control				RNB	Control			
Cuvillon et al. (2007)	RCT	21	41	82.4	85.5%	Hip fracture (not specified)	41.7	25.0	Excluded	Femoral nerve block	IV morphine IV paracetamol
Kullenberg et al. (2004)	RCT	40	40	82.0	63.8 (%)	Femoral neck and pertrochanteric	15.5	15.8	Excluded	Femoral nerve block	Paracetamol and tramadol
Mouzopoulos et al. (2009)	RCT	102	105	72.7	74.4%	Femoral neck and pertrochanteric			Included Patients can be were divided into high- or intermediate risk	Fascia iliaca block	Placebo injection
Nie et al. (2015)	RCT	51	53	70.8	N/A	Hip fracture (not specified)	7.6	7.7	Included Specific data was not available	Fascia iliaca block	IV PCA
Rowlands et al. (2018)	RCT	54	54	83.5	86.4%	Femoral neck			Excluded	Femoral nerve block	IV morphine
Unneby et al. (2020)	RCT	116	120	84.1	64.8%	Femoral neck and pertrochanteric	15.9	16.5	Included Patients can be were divided into with or without dementia	Femoral nerve block	Opioids (not specified)
Uysal et al. (2020)	RCT	46	45	81.7	56.0%	Pertrochanteric			Included Specific data was not available	Femoral nerve block	IV acetaminophen
Yamamoto et al. (2019)	RCT	25	28	84.6	84.9%	Femoral neck and pertrochanteric			Excluded	Fascia iliaca block	IV acetaminophen

RNB: regional nerve block; RCT: randomized controlled trial; IV: intravenous; PCA patient-controlled analgesia; SubQ: subcutaneous.

455 patients received RNB (RNB group) and 486 did not (control group). The fracture locations included the femoral neck and/or pertrochanteric.

Four studies excluded cognitively impaired patients preoperatively [18,19,21,23]. Four studies included cognitively impaired patients. One divided patients into intermediate or high risk [8], whereas another study presented the incidence of delirium depending on whether the patients had dementia or not [9]. Other two studies did not present specific cognition data.

In all the included studies, FIB [8,20,23] or FNB [9,18,19,21,22] was the RNB modality. For pain management in the control group, intravenous/intramuscular/oral opioids or acetaminophen use was reported. The incidence of postoperative delirium varied from 3% to 73%. Patient demographics are described in Table 1.

3.3. Details for method of anesthesia, RNB, and diagnostic tool for delirium

All the studies (except two that did not report the anesthesia method [9,19]) reported the use of general or spinal/epidural anesthesia for fracture surgeries [8,18,20–23]. A landmark-based technique for RNB without ultrasonography and neurostimulator was used in two studies [8,20]. Two studies used ultrasonography [21,23], three used neurostimulators [9,18,19], and one used both ultrasonography and neurostimulator [22]. Five studies [8,18,20–22] adopted repetitive or continuous anesthesia as RNB, and a single RNB or additional one was performed in three studies [9,19,23].

The most commonly used diagnostic tool for delirium was the confusion assessment method in three studies [8,20,23]. The Short Portable Mental Status Questionnaire [19], Diagnostic and Statistical Manual of Mental Disorders, 4th edition [8], Organic Brain Syndrome Scale, Nursing Delirium Screening Scale, Mini-Mental State Examination (MMSE) [9,18], and Delirium Rating Scale-R-98 [22] were used in five studies. One study did not describe the method of diagnosing delirium [21] (Table 2).

3.4. Pain score and medication

Six studies measured pain score using a visual analog scale [8,9,18,19,22,23], numeric rating scale [20], and cumulative pain score [21]. Of these eight studies, two measured pain score at rest and during movement [21,23]. Five studies assessed the amount of pain medication given, such as acetaminophen, pethidine, morphine, and unspecified opioids [8,9,18,20,23]. The details are described in Table 2.

3.5. Risk of bias assessment

Eight included studies had methodological flaws that classified them as either unclear or at high risk of bias for at least one domain [8,9,18–23] (see Figs. 2 and 3). Adequate randomization was reported in three RCTs that used a computer-generated number as the randomization method [8,20,23]. The method of randomization was not reported in the other five RCTs [9,18,19,21,22]. Five trials described the method of allocation concealment [8,9,18,19,23]. One trial used blinding of participants and personnel [8], and another used blinding of outcome assessment [23]. One study was at high risk of bias due to incomplete outcome data with an attrition rate of 3.0%. Furthermore, the investigators did not report the derivation of missing data [21].

3.6. Meta-analysis: The delirium incidence

All eight studies compared the incidence of postoperative delirium between the RNB and control groups. A pooled analysis

Table 2
Details of anesthesia, nerve block, delirium, and pain.

Author (year)	Anesthesia	Technique and dosage of nerve block	Timing of nerve block	Count of block	Diagnostic tool of delirium	Pain score				Other pain medication			
						Method	RNB	Control	*p*-value	Drug	RNB	Control	*p*-value
Cuvillon et al. (2007)	Spinal	Technique: Neurostimulation Bolus: 30 ml of 1.5 % lidocaine Infused: 10 ml/h of 0.2% ropivacaine	Recovery room	Continuous with catheter	Clinical evaluation and MMSE	VAS	< 30	< 30	> 0.05	Opioids (mg)	26	13.4	< 0.01
Kullenberg et al. (2004)	N/A	Technique: Neurostimulation 30 ml of 0.75% ropivacaine	On admission	Single or additional one	SPMSQ	VAS	1.9	2.3	NA		NA	NA	
Mouzopoulos et al. (2009)	Epidural	Technique: Landmark-based 0.3 mL/kg 0.25% bupivacaine	On admission	Repetitive injection	DSM-IV and CAM	VAS	64.6	72.6	0.34	Acetaminophen	0.65	2.3	0.62
										Pethidine	0.48	1.2	
Nie et al. (2015)	General	Technique: Landmark-based Bolus: 20, 25, or 30 mL 0.5% ropivacaine Infused: 0.1 mL/kg/h 0.5% ropivacaine	Operating room	Continuous with catheter	CAM	NRS	NA	NA	0.039	Oral morphine (mg)	7.4	65.8	0.032
Rowlands et al. (2018)	General and spinal	Technique: US-guided Initial dose: 0.5 mL/kg 0.25% levobupivacaine Infused: 5 mL/hour 0.2% ropivacaine	On admission	Continuous with catheter	N/A	Dynamic[a]	19.5	20	0.51		NA	NA	
						Resting[a]	2	5	0.043				
Unneby et al. (2020)	N/A	Technique: Neurostimulation 40 mL 0.25% levobupivacaine	On admission	Single or additional one	OBS, Nu-Desc, and MMSE	VAS	33.6	29.2	0.289	Opioids (mg)	NA	NA	> 0.05
Uysal et al. (2020)	Spinal	Technique: US-guided and neurostimulation Initial dose: 10 mL 0.25% bupivacaine Repetitive dose: 0.5 mL/kg 0.25% bupivacaine	On admission	Intermittent with catheter (3/day)	DRS-R-98	VAS 4PB	3.32	4.47	< 0.01		NA	NA	
						VAS 4PS	3.45	3.22	0.28				
Yamamoto et al. (2019)	Spinal	Technique: US-guided 40 mL 0.25% levobupivacaine	Operating room	Single	CAM	VAS Dynamic	20	40	< 0.01	Analgesic rescue (number)	0.6	0.5	0.65
						VAS Resting	10	20	0.45				

4PB: 4 h after block; 4PS: 4 h after surgery; CAM: Confusion Assessment Method; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSR-R-98: Delirium Rating Scale-R-98; MMSE: Mini-Mental State Examination; NA: Not available; NRS: Numeric Rating Scale; Nu-Desc: Nursing Delirium Screening Scale; OBS: Organic Brain Syndrome Scale; SPMSQ: Short Portable Mental Status Questionnaire; US: Ultrasonography; VAS: Visual Analog Scale.

[a] Cumulative pain score (dynamic or at rest) was used.

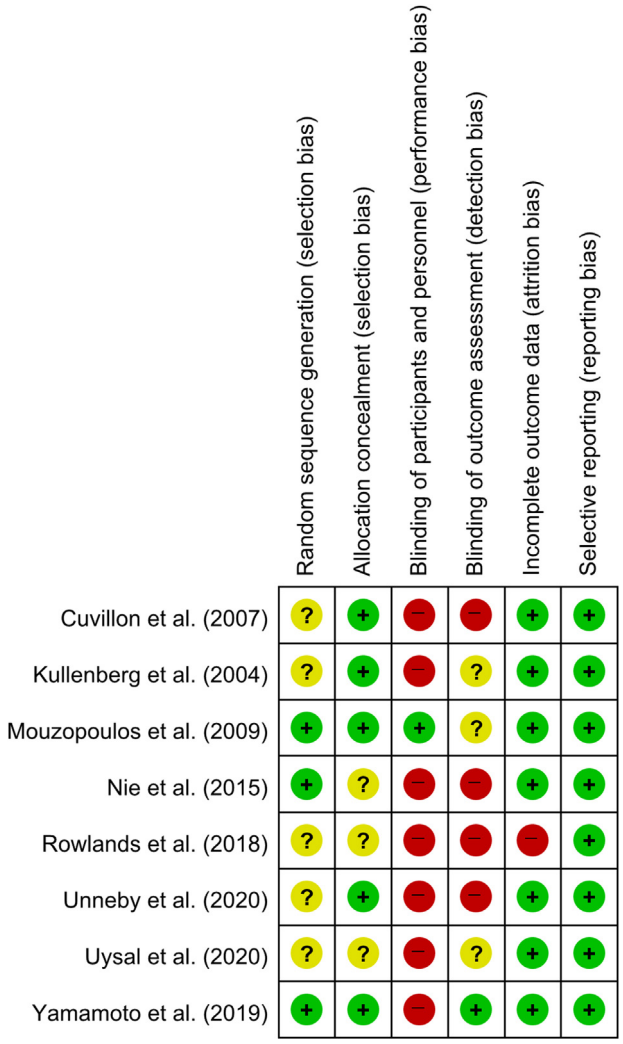

Fig. 2. Summary of risk bias assessment. Reviewers' assessment of each risk of bias item: "+", low risk of bias; "?", unclear risk of bias; and "–", high risk of bias.

revealed no significant differences in delirium incidence between the groups (OR, 0.66; 95% CI: 0.36–1.22; $p = 0.18$). The heterogeneity was considered moderate ($I^2 = 58\%$). A Forest plot is shown in Fig. 4.

Six studies presented the incidence of postoperative delirium between the RNB and control groups for patients without CoI [8,9,18,19,21,23]. Four studies excluded cognitively impaired patients at initial enrollment [18,19,21,23]. Two studies included cognitively impaired patients, and the data from patients without CoI was extracted [8,9]. A pooled analysis demonstrated a significant reduction of delirium incidence in the RNB group compared with the control group (OR, 0.44; 95% CI: 0.21–0.94; $p = 0.03$). The heterogeneity was considered moderate ($I^2 = 51\%$). A Forest plot is shown in Fig. 5.

For the subgroup analyses, we compared the delirium incidence for FIB and FNB separately. We were unable to discern differences in delirium incidence between the groups for FIB (OR, 0.89; 95% CI: 0.19–4.19; $p = 0.88$; $I^2 = 78\%$) and FNB (OR, 0.61; 95% CI: 0.31–1.20; $p = 0.15$; $I^2 = 47\%$; Fig. 6).

4. Discussion

The principal finding of the present study was that RNB reduced the incidence of delirium after hip fracture surgery compared to conventional pain management in patients without preoperative CoI. However, when cognitively impaired patients were included, RNB did not have a preventive effect on perioperative delirium.

Previously, three synthetic studies investigated the effect of RNB for delirium after hip fracture surgeries [24–26]. Two of them reported a significant effect of RNB on reducing postoperative delirium. However, these studies have some questions. First, Abou-Setta et al. [24] reported the effectiveness of RNB to reduce the risk of delirium as present in the RNB group compared to the controls from RCTs (OR = 0.33) and from retrospective cohort studies (OR = 0.24). However, these studies were conducted over a decade ago and included retrospective cohort studies in their analyses. In the present study, we conducted a meta-analysis only with eight recent RCTs to maintain a high level of evidence. Second, Steenberg et al. [25] reported that FIB had a significant protective effect on delirium. However, because they included only two studies, they did not perform a meta-analysis. They simply listed the results of previous studies. In addition, in one of the two (listed) studies, the patient was observed for only 8 h after admission [13].

A previous synthetic study reported by Guay et al. included seven RCTs and did not find a significant effect of RNB on perioperative delirious state. As it was published in 2017, which is relatively recent, our meta-analysis may seem unable to represent a substantial addition on this topic. However, our meta-analysis and that of a previous synthetic study showed several differences. First, they included two studies that investigated only preoperative delirium contrary to the present study, in which postoperative delirium is included. We excluded this study at the full-article reading stage. Second, a study was included that performed psoas compartment block as anesthetic method and compared psoas compartment block with general or spinal anesthesia. Third, after the publication of the above-mentioned synthetic study in 2017, four additional RCTs were reported [9,21–23]. Fourth, for risk stratification, we performed an additional meta-analysis for patients without CoI. By excluding cognitively impaired patients, the present study proved

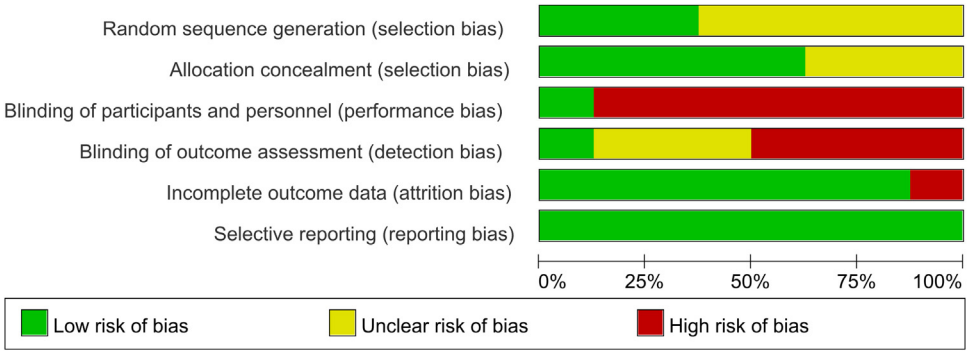

Fig. 3. Risk of bias graph. Reviewer's assessment of each risk bias item, presented as a percentage across all included randomized controlled trials.

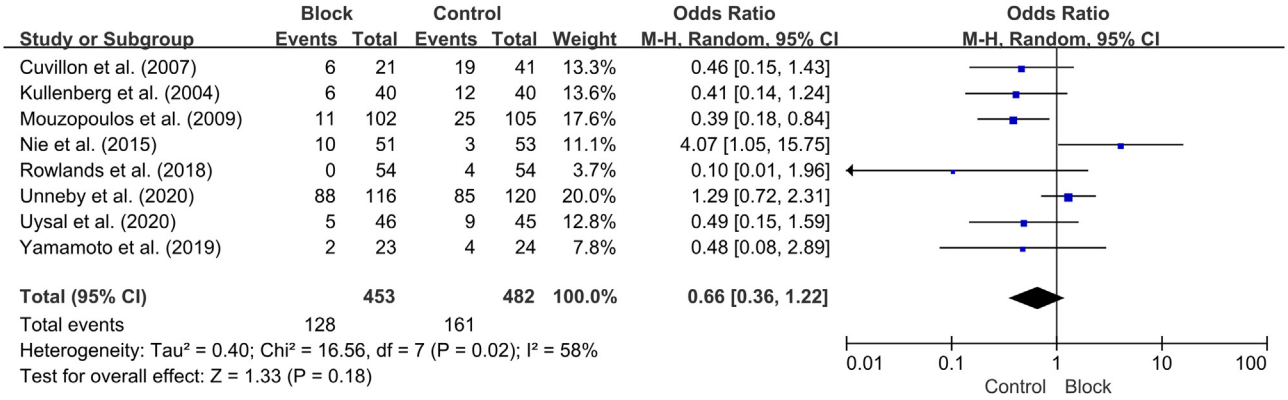

Fig. 4. Results of aggregate analysis from eight RCTs for comparison of the incidence of perioperative delirium according to RNB (including both FIB and FNB) in the general elderly including cognitively impaired patients.

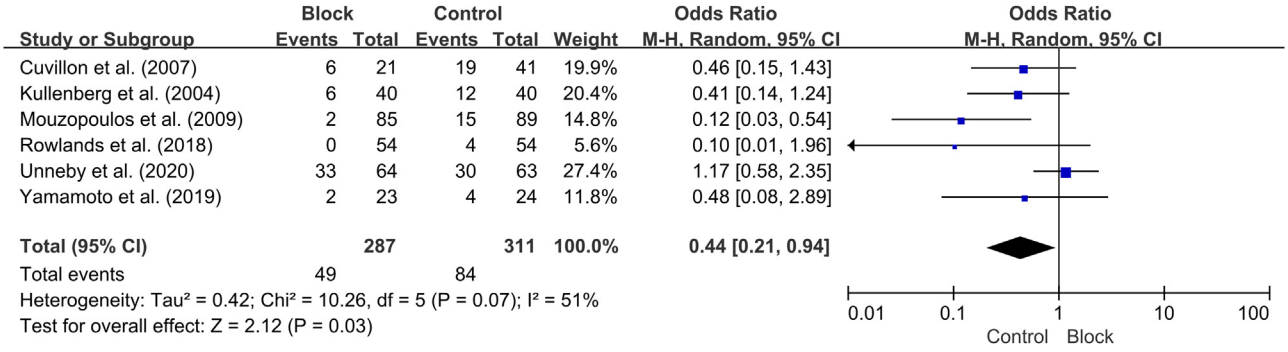

Fig. 5. Results of aggregate analysis of six RCTs for comparison of the incidence of perioperative delirium according to RNB (including both FIB and FNB) in patients without cognitive impairment.

the effectiveness of RNB on perioperative delirium. We believe our meta-analysis is valuable with these differences and additional analysis.

When cognitively impaired patients were combined, RNB did not present the preventive effect for perioperative delirium. There are some possible reasons for these results. First, an incomplete analgesic effect of FIB and FNB may influence our results. Complete pain relief at rest or while performing movements is not achieved by FIB or FNB, which mainly target the femoral, lateral femoral cutaneous, and obturator nerves [24]. Although nociception of the hip joint is innervated mainly from the anterior and superolateral regions [27], FIB and FNB cannot block the obturator nerve, and neither of the techniques blocks the sacral plexus [28]. In addition, cognitively impaired patients are known to have hypersensitivity to pain [29]. There are other known risk factors for postoperative delirium, such as aging, CoI, psychiatric illness, and decreased functional status [5]. Since it was not possible to completely control those risk factors, RNB could not demonstrate a significant preventive effect for delirium.

Among the included RCTs, one study reported a preventive effect of RNB on delirium [8], and other studies did not demonstrate this effect [9,18–23]. Six of the included studies reported a tendency for RNB to prevent delirium; however, none reached statistical significance. Conversely, a study by Nie et al. showed a higher incidence of delirium in the FIB group than the control group (FIB vs. control, 10/51 [19.6%] vs. 3/53 [5.7%], respectively; $p = 0.03$) [20]. They described that the difference in the incidence of delirium was due to predisposing factors in the patients rather than analgesia techniques. Unneby et al. included patients with preoperative dementia, and 96.3% of patients with preoperative dementia had postoperative delirium [9]. We believe these factors may have contributed toward concealing the preventive effect of RNB.

For additional analysis of patients without CoI, studies that did not demonstrate specific CoI data were excluded. In one of the studies by Uysal et al., the average MMSE score was 15.9 in the RNB group and 16.5 in the control group, which means "moderate" CoI [30]. CoI is known as one of the strongest preoperative risk factors for perioperative delirium in hip fracture surgery [3]. After risk stratification, RNB demonstrated a significant preventive effect on postoperative delirium. Four of six studies reported a trend toward pain reduction in the RNB group, although they did not reach statistical significance [8,19,21,23]. In addition to pain reduction, there can be an advantage in avoiding systemic opioids or acetaminophen. However, we cannot conduct synthetic analysis due to the different analgesics and administration methodologies used.

Several concerns have been raised on the reliability of RNB. First, two studies among the included RCTs performed RNB based on landmarks without using supplement equipment [8,20]. Ultrasonography-based and neurostimulator techniques are considered the standard of care in regional anesthesia, which is supported by a report that stated that ultrasonography-based FIB achieved a greater analgesic effect than did FIB without the use of ultrasonography [31]. Second, the appropriate dose should be used to achieve an effective analgesic effect. One of the included study used 10 mL of 0.25% bupivacaine in RNB [22], which is a very low dose for achieving an effective analgesic effect considering that the effective analgesic concentration of 22 mL bupivacaine in 90% of patients was 0.271% [32], even if they dosed 0.5 mL/kg 0.25% bupivacaine three times per day. Hence, dosage should be carefully decided before RNB. The use of ultrasonography or neurostimulator

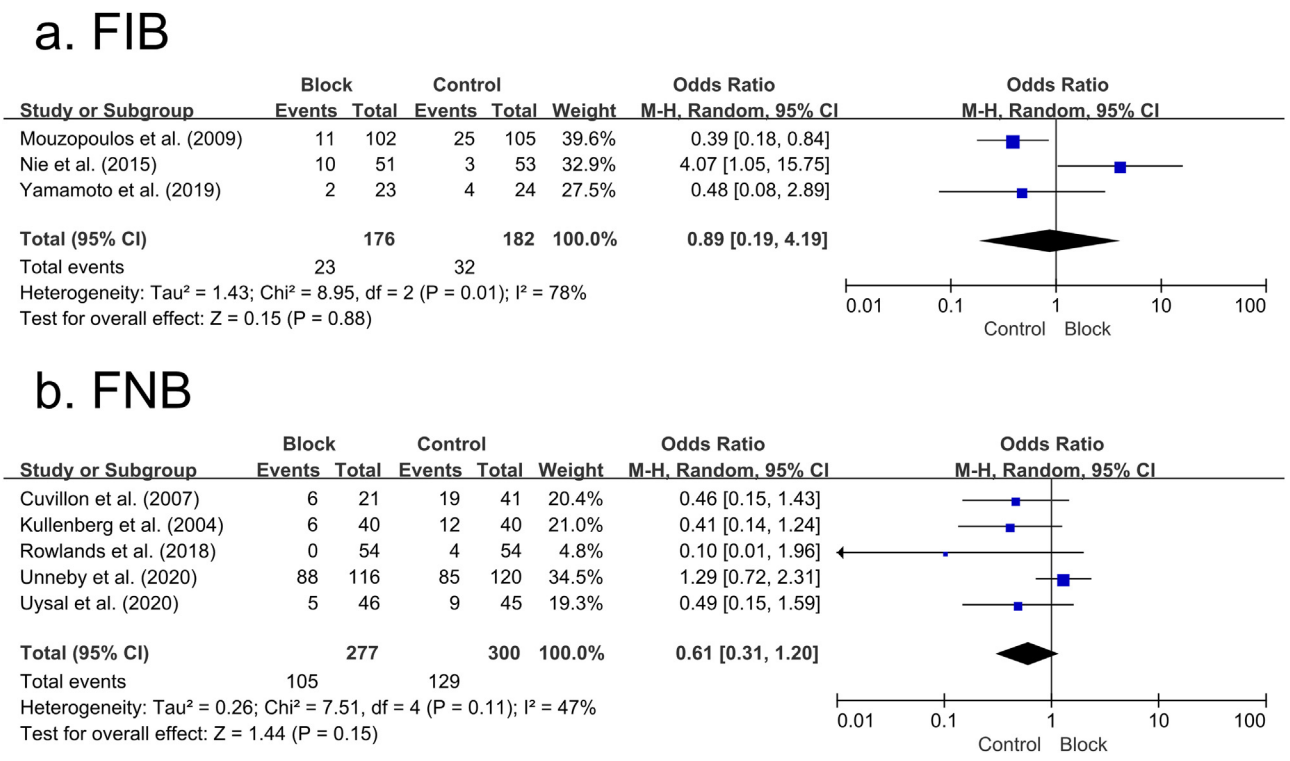

Fig. 6. Results of aggregate analysis for comparison of incidence of perioperative delirium according to: (a) FIB and (b) FNB.

with a carefully selected dosage is recommended for RNB to ensure an analgesic effect.

There were several limitations in this study. First, precise risk stratification was not performed. In addition to CoI, other risk factors for delirium, such as decreased functional status, Foley catheterization, education grade, and complicated medical disease, were not controlled. Second, spinal anesthesia could influence the immediate postoperative pain severity. Pain severity can be influenced by the analgesic effect of spinal anesthesia given persistently from 150 to 420 min [33]. A subanalysis according to anesthesia method could be beneficial in investigating the analgesic effect of RNB, but it was not performed owing to the insufficient data on the anesthesia method and limitations of a review article. Third, dosage, timing, and continuity of nerve block varied according to study. Five studies reported performing nerve block at admission [8,9,19,21,22], and three in the operating room before surgery or in the recovery room immediately postoperatively [18,20,23]. In addition, two studies reported a single or only one additional injection, and four studies used a catheter for continuous infusion. Fourth, screening timing of delirium can influence the result. Although all studies included a postoperative period, one included a preoperative period and another did not clearly describe their screening timing of delirium. Nevertheless, meta-analysis is an appropriate method to generate a higher level of evidence, especially if large cohort studies are not feasible. Indeed, to the best of our knowledge, ours is the first well-structured meta-analysis for this issue.

5. Conclusions

In cases of hip fracture in elderly, RNB demonstrated a preventive effect on perioperative delirium for patients without preoperative CoI. No significant reduction in perioperative delirium was observed when cognitively impaired patients were included.

Disclosure of interest

The authors declare that they have no competing interest.

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Author contribution

Chul-Ho Kim: writing–original draft, formal analysis,
Jae Young Yang: investigation.
Chan Hong Min: data curation.
Hyun-Chul Shon: validation, writing–review & editing.
Ji Wan Kim: methodology, supervision.
Eic Ju Lim: conceptualization, writing–review & editing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.otsr.2021.103151.

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