PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of pericapsular nerve group (PENG) block on perioperative pain management in elderly patients undergoing hip surgical procedures: a protocol for a systematic review with meta-analysis and trial sequential analysis
AUTHORS	Zheng, Jianqiao; Du, Li; Chen, Guo; Zhang, Lu; Deng, Xiaoqian; Zhang, Weiyi

VERSION 1 – REVIEW

REVIEWER	Ng, Tony The University of Hong Kong, Anaesthesiology
REVIEW RETURNED	12-Aug-2022

GENERAL COMMENTS	Thank you for giving me an opportunity to review this meaningful study protocol. Here are my comments and advices: 1. I suggest the authors to consult the journal English editing service to polish the grammar and the use of wordings. 2. Since the authors mentioned most of the literatures about PENG blocks are retrospective studies, would the limitation of the inclusion criteria to RCTs only lead to insufficient number of RCTs for the analysis? If yes, how would you tackle the problem? 3. VAS and NRS are two pain assessment tools with different scales. How do you standardize them for analysis? - some patients in your recruited hip surgery eg hip fracture surgery may not be assessed by VAS and NRS. Instead, they may be assessed by verbal descriptive scale (VDS) or other scales for cognitively impaired elderly, such as PAINAD. How would you solve the problem of different pain assessment tools? 4. How many years of literature will be searched? 5. Would the dose or volume of PENG block of each included study have an impact on the outcomes you proposed?

REVIEWER	Pascarella, Giuseppe Università Campus Bio-Medico di Roma
REVIEW RETURNED	30-Sep-2022

GENERAL COMMENTS	Dear Authors, I read with great attention your article, as it regards one of my favorite topics and field of research. In my opinion, the study protocol is original and well designed. However, I have several minor concerns: - Page 10, line 35. Quadriceps block is defined as a paralysis or paresis of knee extension and hip adduction: this definition is misleading, as hip adduction is provided by iliacus muscle

	For this reason, it should be better to talk about "femoral nerve block", which could be assessed evaluating quadriceps strength (through knee extension) and iliacus muscle strength (through hip adduction). I suggest you to revise this part. - Pag 13, line 20: PENG block targets only articular nerve branches of femoral and obturator nerve and not somatic branches, although the study outcomes include a sensory assessment: It is applied to avoid femoral nerve block? And if so, what somatic area is assessed? - The protocol include a subgroup analysis of the different kind of hip surgery. However, it should be included the possibility to perform a subgroup analysis also regarding the different kind of surgical techniques of hip arthroplasty. If this is not be possible, it should be stated as a possible source of bias.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Tony Ng, The University of Hong Kong, Frankston Pain Management
Comments to the Author:
Thank you for giving me an opportunity to review this meaningful study protocol.
Here are my comments and advices:
1. I suggest the authors to consult the journal English editing service to polish the grammar and the use of wordings.
Revised
2. Since the authors mentioned most of the literatures about PENG blocks are retrospective studies, would the limitation of the inclusion criteria to RCTs only lead to insufficient number of RCTs for the analysis? If yes, how would you tackle the problem?
Clinical practice guidelines are systematic statements designed to help surgeons and patients in taking decisions about appropriate care for specific clinical circumstances. Best evidences of the clinical practice guidelines are systematic review, meta-analysis, and network meta-analysis of RCT with large samples. So, retrospective studies were excluded. In this situation, an insufficient number of RCTs for the meta-analysis may occurred. TSA can be used when Meta-analyses not reaching the required sample size.
Trial sequential analyses (TSA) offers the possibility to evaluate the credibility of statistical results by using statistical monitoring boundaries to determine whether individual trials could be terminated early because the P value was sufficiently small and CI are sufficient to show the desired effect or ineffectiveness. TSA has been performed to assess the risk of type I errors in the cumulative meta-analysis by combining the cumulative Z-curve, the required information size and trial sequential monitoring boundaries.
Z-curve was plotted by each Z-value, which was calculated by the log of the pooled intervention effect from each included study. The P-value is obtained from the Z-value, $|Z| = 1.96$ corresponds to $P=0.05$. The higher Z-values, the lower the P-values. Every time a meta-analysis is updated, a new Z-value is calculated. A series of consecutive Z-values therefore emanates from a series of meta-analysis updates. To inspect the evolution of significance tests, the series of Z-values can be plotted with respect to the accumulated information (accumulated patients, events, or statistical information), thus producing a curve which is commonly referred to as the Z-curve.
Required information size (RIS): In a single randomized trial with a binary outcome measure, the number of events and patients are estimated to allow for reliable statistical inference. That is, a sample size calculated to ensure that a ‘sufficient’ number of events and patients are included. A similar ‘goal post’ is needed for a meta-analysis. This goal post has been referred to as the required meta-analysis information size (IS) or the optimum information size. The required information size

(RIS) defined as the number of participants needed for providing an adequately powered in a meta-analysis to detect or reject a prespecified intervention effect.
RIS based on an a priori anticipated intervention effect, a risk of type I error (α) and type II error (β). The priori anticipated intervention effect (usually expressed as a priori relative risk reduction for dichotomous outcome data and a priori estimate of the difference between means for continuous data) was based on experiences from related areas in clinical topics.
Trial sequential monitoring boundaries (The O'Brien-Fleming boundaries): Trial sequential monitoring boundaries were calculated with the O'Brien-Fleming α-spending function for concluding superiority or inferiority or futility. The O'Brien-Fleming boundaries have been recommended by methodological experts as the preferred choice in most randomized clinical trials where repeated significance testing on accumulating data is performed.
Meta-analyses reaching/or not reaching the required sample size: In meta-analysis, a single significance test can be considered reliable once the required information size is surpassed. To adjust for random error risk, meta-analyses not reaching the required sample size are analyzed with trial sequential monitoring boundaries analogous to interim monitoring boundaries in a single trial. Trial sequential monitoring boundaries adjust the P-value that is required for obtaining a statistical significance according to the number of participants and events in a meta-analysis. The fewer participants and events, the more restrictive the monitoring boundaries are and the lower P-value is required to obtain statistical significance.

Fig. 1. Example of upper half of two-sided trial sequential analysis. The cumulative Z-curve was constructed with each cumulated Z-value calculated after including a new trial according to publication date. Crossing of monitoring boundaries is needed to obtain reliable evidence adjusted for random error risk.
Whether the cumulative Z-curve crossed the monitoring boundary should be judged before the cumulative sample size not reaching the required sample size, as to obtain reliable evidence adjusted for random error risk. Explanations of different results of the trial sequential analysis (upper half of two-sided trial sequential analysis) were seen in figure 2.

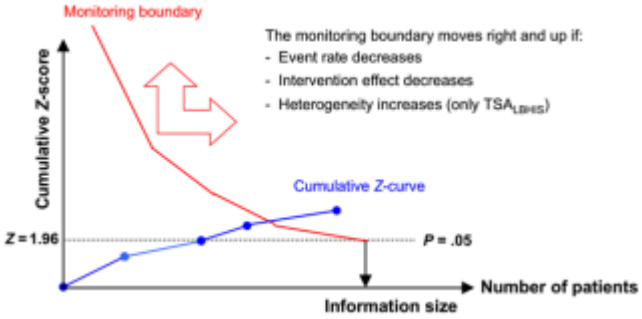
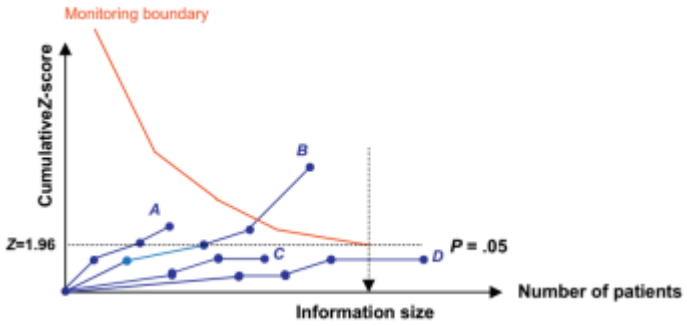


Fig. 2. The cumulative Z-curves (A-D) from four different meta-analyses were constructed.
(A) Crossing of Z= 1.96 provides a ''traditionally'' significant result.
(B) Crossing of the monitoring boundary before reaching the information size is needed to obtain reliable evidence adjusted for random error risk.
(C) Z-curves not crossing Z =1.96 indicate absence of evidence if the information size is not reached.
(D) Z-curves not crossing Z =1.96 indicate absence of evidence and the information size is reached, lack of the predefined intervention effect in this situation.



The proportion of significant (P<0.05) meta-analyses that had:
(1) ''*Potentially spurious evidence of effect*'' that is, the cumulative Z-curve did not cross the monitoring boundaries (Fig. curve A)
(2) ''*Firm evidence of effect''* that is, the cumulative Z-curve crossed the monitoring boundaries (Fig. curve B).
The proportion of nonsignificant (P>0.05) meta-analyses that had:
(1) ''*Absence of evidence*'' that is, the meta-analysis included less patients than the required information size (Fig. curve C)
(2) ''*Lack of effect*'' that is, the meta-analysis included more patients than the required information size (Fig. curve D).
For meta-analyses with ''*potentially spurious evidence of effect*'' or ''*absence of evidence,*'' the additional information size needed to calculate to obtain firm evidence. For meta-analyses with ''*Firm evidence of effect*'', no further trials are needed to obtain firm evidence.
3. VAS and NRS are two pain assessment tools with different scales. How do you standardize them for analysis? - some patients in your recruited hip surgery eg hip fracture surgery may not be assessed by VAS and NRS. Instead, they may be assessed by verbal descriptive scale (VDS) or other scales for cognitively impaired elderly, such as PAINAD. How would you solve the problem of different pain assessment tools?

- If the pain assessment reported as the continuous outcome data by the same pain assessment tool, mean differences (MDs) with 95% confidence intervals (CIs) will be used.
- If the pain assessment reported as the continuous outcome data by different assessment tools with different scales, standardized mean differences (SMDs) with 95% confidence intervals (CIs) will be used.
- If the pain assessment reported as the dichotomous outcome data by different assessment tools, such as none, mild, moderate, and severe pain, relative risks (RRs) with 95% CIs will be used.
- If necessary, continuous outcome data by different assessment tools with different scales can be changed to dichotomous outcome data according the reported outcome of the RCTs, such as NRS 0 corresponded to VDS none, NRS 1-4 corresponded to VDS mild, NRS 5-8 corresponded to VDS moderate, and NRS 9-10 corresponded to VDS severe. Then, relative risks (RRs) with 95% CIs will be used.

4. How many years of literature will be searched?
Pericapsular nerve group (PENG) block was first described by Girón-Arango et al in 2018. In our experience, it's easy to make mistakes (such as incomplete retrieval), when a publication date was defined in the advanced search. In this situation, the use of comprehensive search terms is important in literature retrieval. In our protocol, English and Chinese electronic databases will be searched from inception to August 2022 for published literature. Then, comprehensive updating of the literature search results will be performed prior to the final publication of systematic reviews to avoid missing published studies during the systematic review preparation.
5. Would the dose or volume of PENG block of each included study have an impact on the outcomes you proposed?

Thank you very much for your reminding. It is really helpful for us to revise our protocols. We have revised the subgroup analysis and increase the subgroup analysis based on details of the local anesthetic.
The volume of PENG block could really have an impact on the pain intensity, particularly the quadriceps weakness. Girón-Arango et al. used 20 ml local anesthetic with PENG block on 5 patients who underwent hip surgery and reported an average decrease of 7 points in the pain scales of the patients. [1] Ali Ahiskalioglu et al. used 30 ml local anesthetic with PENG block in patient with right leg recurrent varicose veins. However, patient reported significant quadriceps weakness with the inability to achieve a straight leg raise.[2] Cadaveric dissection of injectate spread following pericapsular nerve group block, aims to justify the distribution of injectate spread relative to the articular branches innervating the hip capsule. Both 10 mL and 20 mL injections spread in the defined bursal space between the iliopsoas and anterior hip joint capsule. This spread pattern provides support that pericapsular block captures the articular branches of the femoral, obturator and accessory obturator nerves.[3]
It is deemed possible to apply high volume local anesthetic in the interfascial plane to the region between the psoas tendon and the bone tissue in the plain between anterior inferior iliac spine and iliopubic eminence, to advance from the deep iliopsoas muscle toward the lateral and surround the muscle and reach the lateral femoral cutaneous nerve and continue from the medial of this muscle and reach femoral nerve. [4] The answer to the question whether the PENG block can spread to obturator nerve depends on the volume administered. Iliopectineal fascia, which forms the medial end of the iliac fascia, can be a barrier preventing the local anesthetic to move further medial and reach the obturator nerve in the deep pectineus muscle. However, considering that iliopectineal fascia has a short course in the craniocaudal direction, it can be speculated that application of high-volume local anesthetic with PENG block results in subpectineal obturator nerve block.
The optimal volume for PENG block remains uncertain, and further study is needed to determine this optimal volume. If sufficient trials are available, the relationship of the local anesthetic volume and the main outcomes will be determined by subgroup analysis based on the data from different type, concentration, dose, volume, and adjuvants of local anesthetics for PENG block.
[1] Giron-Arango L, Peng PWH, Chin KJ, Brull R, Perlas A. Pericapsular nerve group (PENG) block for hip fracture. Reg Anesth Pain Med 2018; 43:859–63.
[2] Ahiskalioglu A, Aydin ME, Ahiskalioglu EO, Tuncer K, Celik M. Pericapsular nerve group (PENG) block for surgical anesthesia of medial thigh. J Clin Anesth 2019; 59:42–3.
[3] Tran J, Agur A, Peng P. Is pericapsular nerve group (PENG) block a true pericapsular block? Reg Anesth Pain Med. 2019 Jan 11: rapm-2018-100278.
[4] Ahiskalioglu A, Aydin ME, Celik M, Ahiskalioglu EO, Tulgar S. Can high volume pericapsular nerve group (PENG) block act as a lumbar plexus block? J Clin Anesth 2020; 61:109650.
Reviewer: 2
Dr. Giuseppe Pascarella, Università Campus Bio-Medico di Roma
Comments to the Author:
Dear Authors,
I read with great attention your article, as it regards one of my favorite topics and field of research.
In my opinion, the study protocol is original and well designed.
However, I have several minor concerns:
- Page 10, line 35. Quadriceps block is defined as a paralysis or paresis of knee extension and hip adduction: this definition is misleading, as hip adduction is provided by iliacus muscle. For this reason, it should be better to talk about "femoral nerve block", which could be assessed evaluating quadriceps strength (through knee extension) and iliacus muscle strength (through hip adduction). I suggest you to revise this part.
Yes, revised.
- Pag 13, line 20: PENG block targets only articular nerve branches of femoral and obturator nerve and not somatic branches, although the study outcomes include a sensory assessment: It is applied to avoid femoral nerve block? And if so, what somatic area is assessed?

Yes, we agree with your opinion. PENG block has the potential advantage of reducing postoperative pain without motor-blocking. But in some case reports, high volume PENG block even presenting as the effect of lumbar plexus block.
Case one: 30 ml of local anesthetic solution (15 ml 0.5% bupivacaine and 15 ml 2% lidocaine) was injected between the psoas tendon and the pubic ramus. After 5 min, sensory testing of the femoral nerve, obturator nerve and lateral femoral cutaneous nerve dermatomes revealed a sufficient level of anesthesia. [1]
Case two: PENG block was applied with 15 ml 0.5% bupivacaine plus 15 ml 2% lidocaine (total volume: 30 ml). In the sensory examination performed 20 min later, sensory loss was noted in the lateral femoral cutaneous, genitofemoral, anterior femoral cutaneous, obturator, and saphenous nerves. Moreover, patient reported significant quadriceps weakness with the inability to achieve a straight leg raise. [2]
Case there: PENG block was applied on the patient with total volume of 30 ml (15 ml 0.5% bupivacaine +15 ml 2% lidocaine). VAS score decreased to 1 within 10 min after the application. After 20 min, sensory testing of the femoral, obturator, lateral femoral cutaneous, and genitofemoral nerves dermatomes revealed a sufficient level of anesthesia. [2]
It is deemed possible to apply high volume local anesthetic in the interfascial plane to the region between the psoas tendon and the bone tissue in the plain between anterior inferior iliac spine and iliopubic eminence, to advance from the deep iliopsoas muscle toward the lateral and surround the muscle and reach the lateral femoral cutaneous nerve and continue from the medial of this muscle and reach femoral nerve. [2] The answer to the question whether the PENG block can spread to obturator nerve depends on the volume administered. Iliopectineal fascia, which forms the medial end of the iliac fascia, can be a barrier preventing the local anesthetic to move further medial and reach the obturator nerve in the deep pectineus muscle. However, considering that iliopectineal fascia has a short course in the craniocaudal direction, it can be speculated that application of high-volume local anesthetic with PENG block results in subpectineal obturator nerve block.
In our protocol, perioperative sensory block was considered as the exploratory outcomes. Sensory block was evaluated using a 3-point scale [0=no block, 1=analgesia (patient can feel touch, not cold), 2=anesthesia (patient cannot feel touch)], which was assessed in the anterior, lateral and medial aspects of the mid-thigh. Our aim is to justify whether high volume pericapsular nerve group (PENG) block could act as a lumbar plexus block, and has the effect of sensory block in special somatic area by the data from RCTs. In actual, gray zone of PENG block still remains. [3] So, we try our best to provided more detail information of PENG block by meta-analysis.
[1] Yu HC, Moser JJ, Chu AY, Montgomery SH, Brown N, Endersby RVW. Inadvertent quadriceps weakness following the pericapsular nerve group (PENG) block. Reg Anesth Pain Med 2019; 44(5):611-3.
[2] Ahiskalioglu A, Aydin ME, Celik M, Ahiskalioglu EO, Tulgar S. Can high volume pericapsular nerve group (PENG) block act as a lumbar plexus block? J Clin Anesth 2020; 61:109650.
[3] Mistry T, Sonawane KB. Gray zone of pericapsular nerve group (PENG) block. J Clin Anesth 2019; 58:123-124.
- The protocol includes a subgroup analysis of the different kind of hip surgery. However, it should be included the possibility to perform a subgroup analysis also regarding the different kind of surgical techniques of hip arthroplasty. If this is not be possible, it should be stated as a possible source of bias.
Yes, we agree with your opinion. it is really necessary to perform the subgroup analysis based on different kind of hip disease or different kind of surgical techniques of hip surgery, including hip arthroplasty. In our protocol, we listed this item as “if sufficient trials are available, ...different types of hip disease or surgery..... ..... will be analyzed independently”. And it may not be well expressed. Then, we revised our expression in this item, as follows in the protocol.
► Different types of hip disease or different kind of surgical techniques of hip surgery (hip disease, such as hip fracture and hip osteoarthritis; hip surgery such as different kind of surgical techniques of hip arthroplasty, hip fracture fixation and hip arthroscopy procedures).

VERSION 2 – REVIEW

REVIEWER	Ng, Tony The University of Hong Kong, Anaesthesiology
REVIEW RETURNED	01-Nov-2022

GENERAL COMMENTS	Thank you for giving me the opportunity to review this manuscript again. This version has been much improved. Here are some minor comments on typos/use of English: p7 line 30 scarce instead of rare p12 line 28 Patient recovery instead of Patient's recovery p13 line 22 Block end time instead of Block ended time Thank you.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Tony Ng, The University of Hong Kong, Frankston Pain Management
Comments to the Author:
Here are some minor comments on typos/use of English:
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Revised
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