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Title: Comparison of effects of four treatment methods for unstable intertrochanteric fractures：a network meta-analysis

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Abstract

Purpose: The optimal internal fixation device for unstable intertrochanteric fracture remains a matter of controversy. By performing network meta-analysis, we developed a ranking of the following four surgical methods: proximal femoral nail antirotation, InterTan nail, gamma nail (GN) and sliding hip screws. We compare the complication rates in patients with unstable intertrochanteric fractures.

Materials and Methods: After an exhaustive search of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials for relevant studies, randomized controlled trials meeting selection criteria were entered into our network meta-analysis. Statistical analyses were conducted using Stata software, version 13.0 (Stata Corporation, College Station, Texas, USA).

Results: We included 12 randomized controlled trials. Compared to Sliding hip screw, there were no substantial differences in rates of complications in unstable intertrochanteric fractures patient undergoing various treatments (all $p > 0.05$). Nevertheless, the surface under the cumulative ranking curve (SUCRA) for GN (80.6%) was significantly higher than those of the other three methods.

Conclusion: GN had the highest probability of reducing the total incidence of complications among the four interventions for treating unstable intertrochanteric fractures.

Keywords: unstable femoral intertrochanteric fractures; proximal femoral nail antirotation; gamma nail; sliding hip screws; interTan nail; network meta-analysis.

1. Introduction

Intertrochanteric fractures are common in the elderly [1]. Operative treatment, permitting immediate postoperative weight-bearing and reducing complications, is gradually becoming preferred. Sliding hip screw (SHS) is used extensively for treating intertrochanteric fractures. This internal fixation device is considered the "gold standard technique" for treating such fractures [2,3]. Nevertheless, the optimal internal fixation device for repair of unstable intertrochanteric fractures (UIF) (AO/OTA 31-A2 and 31-A3) remains a matter of controversy [4]. The common fixation methods for unstable intertrochanteric fractures include interTan nail (IT), proximal femoral nail antirotation (PFNA), gamma nail (GN) and sliding hip screws (SHS). Several traditional meta-analysis have compared various interventions to treat UIF [4–7]. Nevertheless, these studies were inconclusive. In addition, traditional meta-analysis can only directly compare two interventions, and therefore they cannot comprehensively estimate more than three interventions. However, network meta-analysis can be used to compare several interventions even if there are no head-to-head comparisons [8].

Therefore, we carried out a network meta-analysis to assess the relative effects of four common surgical interventions, including GN, PFNA, IT and SHS, to suggest the optimal internal fixation device for UIF based on complication rates.

2. Materials & Methods

This meta-analysis was created according ot PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines [9]. The work has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines[10]**.**

2.1 Study selection

Inclusion criteria: 1) average age greater than 60 with unstable intertrochanteric fractures; 2) interventions and comparison included PFNA, SHS, GN and IT; 3) outcomes included mortality, cutout, later fracture, non-union, superficial wound infection and embolism; 4) randomized controlled trials; and 5) minimum follow-up 12 months. Exclusion criteria were as follows: 1) duplicate publications; 2) non-human study; 3) lack of relevant data; 4) pathologic fracture; 5) non-RCT, review articles, conference abstracts, letters or case reports; and 6) animal studies, biomechanical studies, cadaveric or model studies.

2.2 Literature search

We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (up to March 30, 2018). The search strategies are shown in Supplemental List 1. To ensure completeness, we also searched for the bibliographies of relevant literature by undertaking manual search.

2.3 Data extraction

Two authors (W.B.S. and X.B.Z.) independently extracted the data, and differences were resolved through discussion with a third author (H.H.W.). The extracted information included age, number of cases, primary author, interventions, year, country, follow-up period and complications. Primary outcomes as complications (e.g. mortality, cutout, later fracture, non-union, superficial wound infection and embolism). We count the total number of complication for each group and compared the total number of complications between different group.

2.4 Risk of bias assessment

Two investigators (H.Y.L. and X.B.Z.) evaluated the methodological quality of the included literature using the Cochrane Collaboration tool.

2.5 Statistical analysis

All analyses employed STATA statistical software (Version 13.0, Stata Corporation,College

Station, Texas, USA). We calculated the relative risk (RR) with 95% confidence intervals (95% CI) to evaluate the dichotomous variables. We used the Z-test to measure the pooled effect size [11]. Heterogeneity was assessed using Chi^2 tests and I^2 statistic. $I^2 > 50\%$ demonstrated significantly statistical heterogeneity, in which case a fixed-effect model was applied, otherwise, a random-effect model was applied [12,13]. $P < 0.05$ indicated significant statistical difference. A network meta-analysis merges direct evidence and indirect evidence or different indirect evidence simultaneously [14]. **Multivariate meta-analysis and meta-regression were applied in the statistical analysis**[15,16]**.** In each closed loop, the inconsistency factor (IF) was used to assess heterogeneity. If the 95% CI of IF reached zero, it was suggested that there no significant statistical difference [17]. In our study, funnel plots were used to assess whether there were small-study effects [18]. The assumption of consistency models allowed the existence of heterogeneity of the intervention effects among all studies, although there were no substantial differences in study design. The most frequent method was utilized to calculate the ranking probabilities for the fitted model after the generation of heterogeneity matrix [19]. The surface under the cumulative ranking probabilities (SUCRA) was used to rank the four interventions for treating UIF. A higher SUCRA means better results for the respective intervention [20]. Sensitivity analyses were performed by excluding one study and recalculation of the pooled estimate.

3. Results

3.1 Baseline characteristics of included studies

A total of 3,327 potential records were reviewed from the databases; 1,818 duplicate records were excluded. We excluded 1,317 records after reviewing titles and abstracts. A total of 182 records were screened through by reviewing the full texts. Finally, 12 articles were included in our network meta-analysis [1,17–27]. Two studies included both unstable and stable fractures [22,29], however, the results were reported separately, therefore, we extracted the data of unstable fractures. Four kinds of internal fixations: sliding hip screws (SHS), proximal femoral nail antirotation (PFNA), interTan nail (IT) and gamma nail (GN) were used in the 12 trials. The selection process is summarized in Figure 1. Table 1 provides a summary of the included studies. The total number of participants was 1,289. These studies were published between 1992 and 2016. Figure 2 shows the risk of bias summary of the selected articles.

3.2 Evidence network

Figure 3 shows the evidence network. Connecting lines indicate direct comparison between the two connected interventions, and pairs of interventions without connection can be compared indirectly through network meta-analysis. The width of lines represents the number of trials. The size of nodes corresponds to the overall sample size of the intervention(GN, PFNA, SHS and IT).

3.3 Contribution plot of network meta-analysis

The contribution of each direct comparison to the assessment of the network overall effects is shown in Figure 4: (1) two included studies directly compared GN and IT, whose percentage contribution to GN versus IT, GN versus PFNA, GN versus SHS, IT versus PFNA, IT versus SHS and PFNA versus SHS were 7.3%, 8.1%, 2.0%, 3.4%, 5.3%, and 5.2% and 5.5% for the total network meta-analysis, respectively; (2) two studies directly compared GN and PFNA, whose percentage contribution to GN versus IT, GN versus PFNA, GN versus SHS, IT versus PFNA, IT versus SHS and PFNA versus SHS were 28.7%, 44.1%, 10.4%, 3.4%, 19.7%, and 28.9% and 23.9% for the total network meta-analysis, respectively; (3) five study directly compared GN and SHS, whose percentage contribution to GN versus IT, GN versus PFNA, GN versus SHS, IT versus PFNA, IT versus SHS and

PFNA versus SHS were 12.7%, 18.4%, 75.1%, 0%, 25.0%, and 34.1% and 26.3% for the total network meta-analysis, respectively; (4) two studies directly compared IT and PFNA, whose percentage contribution to GN versus IT, GN versus PFNA, GN versus SHS, IT versus PFNA, IT versus SHS and PFNA versus SHS were 38.6%, 10.9%, 0%, 90.3%, 33.2%, and 8.9% and 29.0% for the total network meta-analysis, respectively; (5) one study directly compared IT and SHS, whose percentage contribution to GN versus IT, GN versus PFNA, GN versus SHS, IT versus PFNA, IT versus SHS and PFNA versus SHS were 2.7%, 2.9%, 2.1%, 1.5%, 3.3%, and 3.7% and 2.9% for the total network meta-analysis, respectively; (6) two studies directly compared PFNA and SHS, whose percentage contribution to GN versus IT, GN versus PFNA, GN versus SHS, IT versus PFNA, IT versus SHS and PFNA versus SHS were 10.0%, 15.6%, 10.4%, 1.5%, 13.5%, and 19.3% and 12.5% for the total network meta-analysis, respectively.

3.4 Evaluating and presenting assumptions of network meta-analysis

An inconsistency plot was employed to evaluate the heterogeneity among studies in a closed loop of this network meta-analysis (Figure 5). This network meta-analysis was composed of 4 triangular loops, including: GN- IT - PFNA loop, IT - PFNA - SHS loop, GN - PFNA- SHS loop and GN - IT - PFNA loop. The 95% CI of IF value reached zero, demonstrating no substantial inconsistency. All P > 0.05, further suggesting that the indirect and direct comparisons of the 4 internal fixations were consistent.

3.5 Publication bias and sensitivity analyses

Assessment of publication bias (Figure 6) suggested that all included studies were roughly symmetrically distributed around the vertical line (x= 0), indicating that publication bias for the included literature was acceptable (Figure 6). Overall, sensitivity analyses did not change the results

(Supplemental List 2 and Supplemental List 3).

3.6 Comparison of complication rates

Network meta-analysis demonstrated no significant differences in the incidences of complication between SHS, PFNA, GN and IT (GN vs SHS : RR = 0.91; 95% CI, 0.53–1.56; IT vs SHS: RR = 1.33; 95% CI, 0.60–2.95; PFNA vs SHS: RR = 1.50; 95% CI, 0.74–3.07; IT vs GN: RR = 1.47; 95% CI, 0.69–3.12; PFNA vs GN: RR = 1.66; 95% CI, 0.85–3.24; PFNA vs IT: RR = 1.13; 95% CI, 0.75–1.17; Figure 7).

3.7 Ranking of treatments

Ranking graphs of the distribution of probabilities of total complication are displayed in Figure 8. The direct and indirect comparisons indicated that GN significantly decreased the incidence of total complications compared to IT, PFNA and SHS. The SUCRA probabilities were 37.0% for IT, 80.6% for GN, 15.7% for PFNA and 66.6% for SHS (Figure 8).

4. Discussion

The best treatment for UIF remains a topic of debate. SHS and intramedullary nail are the primary internal fixation devices. Recently, several traditional meta-analyses of the treatment of intertrochanteric fractures have been published [4–7]. Most studies focused on the comparison between two interventions. However, the use of traditional meta-analysis methods to analyze present data is a challenging task because there are four interventions.

To the best of our knowledge, this is the first network meta-analysis of four treatments of UIF. Our aim was to rank four different internal fixations (GN, PFNA, SHS and IT) in terms of their associated complications for treating unstable intertrochanteric fractures. We found no substantial difference in the rates of complications among GN, PFNA, SHS and IT. The SUCRA value of GN was 80.6%, substantially higher than those of the other three internal fixations. Greater SUCRA values suggest higher rank of the intervention [20]. However, the relative risk (RR) of any complications was lower in GN compared to the other alternatives. SHS had a lower complication rate than did PFNA or IT. PFNA had a higher complication rate than did the other alternatives. Furthermore, IT had a higher complication rate than did SHS. We conclude that GN has the highest probability of reducing the total incidence of complications among the four interventions for treating unstable intertrochanteric fractures.

SHS, GN, and PFNA have been most commonly used to treat intertrochanteric fractures over the last decade [32,33]. The InterTAN nail is a relatively new device [34]. Intramedullary nailing has the advantages of minimal invasiveness, short operation time, less bleeding and rapid rehabilitation [35]. Many studies showed that unstable intertrochanteric fractures are best treated with intramedullary nailing [36–38]. However, other studies reported that substantial differences between the intramedullary nail and SHS in terms of clinical outcome [1,4]. Our findings demonstrated that there were no substantial differences between SHS and intramedullary nailing in terms of complication.

Gamma nail (GN) is characterized by the need for reaming and the use of a lag screw. In proximal femoral nail antirotation (PFNA), there is no need for reaming with an antirotational helical blade. For the InterTAN nail (IT), there is a reamed nail with an integrated interlocking lag and compression screws. Due to its capability of preventing rotation of femoral head, PFNA was the best internal fixation devices for treating UIF [39]. Some biomechanical studies indicated that the helical blade system significantly increased stability in treating UIF compared to the conventional lag screw [40,41]; furthermore, a biomechanical study reported that the InterTAN intramedullary nail had advantages for treating UIF compared with PFNA [42], and the InterTAN system bore higher loads in treating UIF compared to the single-screw system (GN) [43]. Vaquero et al. reported that the rates of local postoperative complications were similar among PFNA and GN groups [31]. Zehir et al. reported that complication rates were similar among PFNA and InterTAN groups [44]. Zhang et al. reported that there were no substantial differences in general complications among PFNA and InterTAN groups [30]. Wu et al. reported that there was no significant difference in the total complication rate between the IT and GN groups; however, the incidence of cut-out in GN group was higher than that of the IT group [45]. Our network analysis showed that the GN technique had no significant difference between PFNA, IT and SHS according to the RR values. The SUCRA percentage showed that GN had a lower probability of complications than did PFNA or IT.

The meta-analysis by Wang. et al. [46] addressed similar questions. Nevertheless, it presented some differences from our study. The SUCRA scores was similar between PFNA group and GN group in the Wang et al, which compared three fixation modalities in nine studies. We compared four fixation modalities in 12 studies. Our meta-analysis added three RCTs and compared four fixations, providing a more up-to-date source of information than the Wang et al. More study is included and the conclusion is more reliable. The network meta-analysis could combine direct evidence with indirect evidence to increase the credibility of evidence by comparing the same control measure. In our study, the contribution of PFNA vs IT to the entire network was obviously more than the contribution of GN vs IT. However, PFNA group had a higher complication rate compared to IT group and GN group had a lower complication rate compared to IT group. This may explain why GN was found to be superior method in our study. Furthermore, our meta-analysis follows PRISMA guidelines, making it convenient for clinicians, whereas, the meta-analysis by Wang et al. did not mention it.

There were several strengths in this network meta-analysis: 1) we compared treatment strategies indirectly; when no head-to-head trial existed, more precise efficacy estimates were based on direct and indirect comparisons with various interventions; 2) SUCRA and posterior probabilities of outcomes were used to distinguish subtle differences among four treatments; and 3) the 95% confidence intervals of inconsistency factor values reached zero, demonstrating no substantial inconsistency. Nevertheless, this analysis has several limitations: 1) despite our exhaustive search, only 12 studies were included in this systematic review. The sample sizes of RCTs that were included in the present study were very small; 2) this study only focused on adverse events. We did not take into consideration other outcomes, including functional scores and radiological outcomes as these are not always reported or are reported in various ways; 3) due to substantial difference in the postoperative X-ray images among GN, PFNA, SHS and IT, the term "blinding of outcome assessment" was assessed as "high risk" for all 12 studies; and 4) Although all studies were RCTs, the qualities of the recruited studies were quite variable. Some studies were unclear as to randomization sequence generation; some had weak blinding, or imperfect allocation concealment; therefore, selection bias or confounding factors might be present, influencing our results. This limitation might be resolved by an updated network meta-analysis restricted to high quality studies, once sufficient become available.

5. Conclusion

GN has the highest probability of reducing the total incidence of complications among the four interventions for treating unstable intertrochanteric fractures. Our result needs to be validated by more high-quality RCT studies with larger sample sizes.

Provenance and peer review

Not commissioned, externally peer-reviewed

References

[1] Reindl, Rudolf, Harvey, J. Edward, Berry, K. Gregory, Rahme, Elham, Intramedullary Versus Extramedullary Fixation for Unstable Intertrochanteric Fractures: A Prospective Randomized Controlled Trial, J. Bone Jt. Surg. Am. Vol. 97 (2015) 1905–1912.

[2] P. Fröhlich, T. Benkö, [DHS (Dynamic Hip Screw)-osteosynthesis in the management of femoral fractures in the hip region and the place of this method in the treatment of such injuries], Magy Traumatol Ortop Kezseb Plasztikai Seb. 36 (1993) 59–64.

[3] M.T. Clayer, R.J. Bauze, Morbidity and mortality following fractures of the femoral neck and trochanteric region: analysis of risk factors, J. Trauma. 30 (1990) 1419–1420.

[4] M.J. Parker, H.H. Handoll, J.M. Queally, E. Harris, H.H. Handoll, M.J. Parker, Intramedullary nails for extracapsular hip fractures in adults, John Wiley & Sons, Ltd, 2014.

[5] L. Nherera, P. Trueman, A. Horner, T. Watson, A.J. Johnstone, Comparison of a twin interlocking derotation and compression screw cephalomedullary nail (InterTAN) with a single screw derotation cephalomedullary nail (proximal femoral nail antirotation): a systematic review and meta-analysis for intertrochanteric frac, J Orthop Surg Res. 13 (2018) 46. doi:10.1186/s13018-018-0749-6.

[6] Q. Zhu, X. Xu, X. Yang, X. Chen, L. Wang, C. Liu, P. Lin, Intramedullary nails versus sliding hip screws for AO/OTA 31-A2 trochanteric fractures in adults: A meta-analysis, Int. J. Surg. (2017).

[7] A.B. Li, W.J. Zhang, J. Wang, W.J. Guo, X.H. Wang, Y.M. Zhao, Intramedullary and extramedullary fixations for the treatment of unstable femoral intertrochanteric fractures: a

meta-analysis of prospective randomized controlled trials, Int Orthop. 41 (2017) 403–413. doi:10.1007/s00264-016-3308-y.

[8] D.M. Caldwell, A.E. Ades, J.P. Higgins, Simultaneous comparison of multiple treatments: combining direct and indirect evidence, Bmj. 331 (2005) 897.

[9] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement., J. Clin. Epidemiol. 62 (2009) 1006–1012. doi:10.1016/j.jclinepi.2009.06.005.

[10] B.J. Shea, B.C. Reeves, G. Wells, M. Thuku, C. Hamel, J. Moran, D. Moher, P. Tugwell, V. Welch, E. Kristjansson, D.A. Henry, AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both., BMJ. 358 (2017) j4008.

[11] H. Chen, A.K. Manning, J. Dupuis, A method of moments estimator for random effect multivariate meta-analysis, Biometrics. 68 (2012) 1278–1284.

[12] J.L. Peters, A.J. Sutton, D.R. Jones, K.R. Abrams, L. Rushton, Comparison of two methods to detect publication bias in meta-analysis, Jama J. Am. Med. Assoc. 295 (2006) 676–680.

[13] E. Zintzaras, J.P.A. Ioannidis, Heterogeneity testing in meta ‐ nalysis of genome searches, Genet. Epidemiol. 28 (2005) 123–137.

[14] A. Chaimani, J.P. Higgins, D. Mavridis, P. Spyridonos, G. Salanti, Graphical tools for network meta-analysis in STATA, PLoS One. 8 (2013) e76654.

[15] I.R. White, Network meta-analysis, Stata J. 15 (2015) 951–985. http://www.stata-journal.com/article.html?article=st0410.

[16] G. Salanti, J.P.T. Higgins, A.E. Ades, J.P.A. Ioannidis, Evaluation of networks of randomized

trials., Stat. Methods Med. Res. 17 (2008) 279–301. doi:10.1177/0962280207080643.

[17] F. Song, D.G. Altman, A.M. Glenny, J.J. Deeks, Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses, Bmj. 326 (2003) 472.

[18] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, Bmj. 315 (1997) 629–634.

[19] I.R. White, J.K. Barrett, D. Jackson, J.P.T. Higgins, Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression., Res. Synth. Methods. 3 (2012) 111–125. doi:10.1002/jrsm.1045.

[20] G. Salanti, A.E. Ades, J.P.A. Ioannidis, Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 64: 163-71, J. Clin. Epidemiol. 64 (2011) 163–171.

[21] I. Aktselis, C. Kokoroghiannis, E. Fragkomichalos, G. Koundis, A. Deligeorgis, E. Daskalakis, J. Vlamis, N. Papaioannou, Prospective randomised controlled trial of an intramedullary nail versus a sliding hip screw for intertrochanteric fractures of the femur, Int. Orthop. 38 (2014) 155–161.

[22] M. Seyhan, I. Turkmen, K. Unay, A.T. Ozkut, Do PFNA devices and Intertan nails both have the same effects in the treatment of trochanteric fractures? A prospective clinical study, J Orthop Sci. 20 (2015) 1053–1061. doi:10.1007/s00776-015-0750-4.

[23] K.S. Leung, W.S. So, W.Y. Shen, P.W. Hui, Gamma nails and dynamic hip screws for peritrochanteric fractures. A randomised prospective study in elderly patients, J. Bone Jt. Surg. Br. Vol. 74 (1992) 345.

[24] T.M. Barton, R. Gleeson, C. Topliss, R. Greenwood, W.J. Harries, T.J. Chesser, A comparison of the long gamma nail with the sliding hip screw for the treatment of AO/OTA 31-A2 fractures of the proximal part of the femur: a prospective randomized trial, J. Bone Jt. Surg. Am. Vol. 92 (2010) 792–798.

[25] H. S., R. Wirbel, I. Ojodu, A. Pizanis, T. Pohlemann, J. Fleischer, Does the implant make the difference ? - Prospective comparison of two different proximal femur nails, Acta Orthop. Belg. 82 (2016) 319–331. http://131.211.208.19/login?auth=eng&url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=27682295.

[26] Y. Xu, D. Geng, H. Yang, G. Zhu, X. Wang, Comparative study of trochanteric fracture treated with the proximal femoral nail anti-rotation and the third generation of gamma nail, Inj. J. Care Inj. 41 (2010) 1234–1238.

[27] Y.Z. Xu, D.C. Geng, H.Q. Mao, X.S. Zhu, H.L. Yang, A comparison of the proximal femoral nail antirotation device and dynamic hip screw in the treatment of unstable pertrochanteric fracture, J. Int. Med. Res. 38 (2010) 1266.

[28] S. Papasimos, C.M. Koutsojannis, A. Panagopoulos, P. Megas, E. Lambiris, A randomised comparison of AMBI, TGN and PFN for treatment of unstable trochanteric fractures, Arch. Orthop. Trauma Surg. 125 (2005) 462–468.

[29] J. Zou, Y. Xu, H. Yang, A comparison of proximal femoral nail antirotation and dynamic hip screw devices in trochanteric fractures, J. Int. Med. Res. 37 (2009) 1057–1064.

[30] S. Zhang, K. Zhang, Y. Jia, B. Yu, W. Feng, InterTan nail versus Proximal Femoral Nail Antirotation-Asia in the treatment of unstable trochanteric fractures, Orthopedics. 36 (2013)

e288.

[31] J. Vaquero, J. Munoz, S. Prat, C. Ramirez, H.J. Aguado, E. Moreno, M.D. Perez, Proximal Femoral Nail Antirotation versus Gamma3 nail for intramedullary nailing of unstable trochanteric fractures. A randomised comparative study, Inj. J. Care Inj. 43 (2012) S47.

[32] C. Kammerlander, F. Gebhard, C. Meier, A. Lenich, W. Linhart, B. Clasbrummel, T. Neubauer-Gartzke, M. Garcia-Alonso, T. Pavelka, M. Blauth, Standardised cement augmentation of the PFNA using a perforated blade: A new technique and preliminary clinical results. A prospective multicentre trial, Injury. 42 (2011) 1484–1490. doi:10.1016/j.injury.2011.07.010.

[33] I.B. Schipper, R.K. Marti, der W.C. Van, Unstable trochanteric femoral fractures: extramedullary or intramedullary fixation. Review of literature, Inj. J. Care Inj. 35 (2004) 142.

[34] A.B. Li, W.J. Zhang, J.Q. Wang, Y.M. Zhao, W.J. Guo, Learning Curve and Clinical Outcomes of Performing Surgery with the InterTan Intramedullary Nail in Treating Femoral Intertrochanteric Fractures, Biomed Res. Int. 2017 (2017) 6781070.

[35] C. D'Arrigo, A. Carcangiu, D. Perugia, S. Scapellato, R. Alonzo, S. Frontini, A. Ferretti, Intertrochanteric fractures: comparison between two different locking nails, Int. Orthop. 36 (2012) 2545–2551.

[36] D.C. Hardy, P.Y. Descamps, P. Krallis, L. Fabeck, P. Smets, C.L. Bertens, P.E. Delince, Use of an intramedullary hip-screw compared with a compression hip-screw with a plate for intertrochanteric femoral fractures. A prospective, randomized study of one hundred patients, J. Bone Jt. Surg. Am. Vol. 80 (1998) 618–630.

[37] P.J. Kregor, W.T. Obremskey, H.J. Kreder, M.F. Swiontkowski, Unstable pertrochanteric

femoral fractures, J. Orthop. Trauma. 19 (2005) 63.

[38] R. Stern, Are there advances in the treatment of extracapsular hip fractures in the elderly?, Inj. J. Care Inj. 38 (2007) 77–87.

[39] R.K.J. Simmermacher, J. Ljungqvist, H. Bail, T. Hockertz, A.J.H. Vochteloo, U. Ochs, C.V.D. Werken, The new proximal femoral nail antirotation (PFNA) in daily practice: Results of a multicentre clinical study, Inj. J. Care Inj. 39 (2008) 932–939.

[40] Z. Qian, Y. Xu, X. Wang, D. Geng, T. Tang, Comparison of biomechanical and clinical effects among dynamic hip screw, proximal femur nail antirotation and Gamma3, J. Clin. Rehabil. Tissue Eng. Res. 14 (2010) 8974–8979.

[41] E. Strauss, J. Frank, J. Lee, F.J. Kummer, N. Tejwani, Helical blade versus sliding hip screw for treatment of unstable intertrochanteric hip fractures: a biomechanical evaluation, Inj. J. Care Inj. 37 (2006) 984–989.

[42] Y. Huang, C. Zhang, Y. Luo, A comparative biomechanical study of proximal femoral nail (InterTAN) and proximal femoral nail antirotation for intertrochanteric fractures, Int Orthop. 37 (2013) 2465–2473. doi:10.1007/s00264-013-2120-1.

[43] J. V Nuchtern, A.H. Ruecker, K. Sellenschloh, M. Rupprecht, K. Puschel, J.M. Rueger, M.M. Morlock, W. Lehmann, Malpositioning of the lag screws by 1- or 2-screw nailing systems for pertrochanteric femoral fractures: a biomechanical comparison of gamma 3 and intertan, J Orthop Trauma. 28 (2014) 276–282. doi:10.1097/bot.0000000000000008.

[44] S. Zehir, E. Şahin, R. Zehir, Comparison of clinical outcomes with three different intramedullary nailing devices in the treatment of unstable trochanteric fractures, Ulus. Travma Acil Cerrahi Derg. 21 (2015) 469.

[45] D. Wu, G. Ren, C. Peng, X. Zheng, F. Mao, Y. Zhang, InterTan nail versus Gamma3 nail for intramedullary nailing of unstable trochanteric fractures, Diagn Pathol. 9 (2014) 191. doi:10.1186/s13000-014-0191-y.

[46] H.-H. Wang, W.-B. Shu, G.-H. Lan, X.-B. Zhang, Z.-Q. Jiang, D.-H. Xu, X.-X. Bao, A.-B. Li, Network meta-analysis of surgical treatment for unstable femoral intertrochanteric fractures., Oncotarget. 9 (2018) 24168–24177. doi:10.18632/oncotarget.24202.

Table Caption

Table 1 Characteristics of the included studies.

Figure Caption

Figure 1 Flow chart of article selection for inclusion.

Figure 2 Forest plot showing risk of bias summary.

Figure 3 The evidence network for trials enrolled in this network meta-analysis.

Note: SHS= sliding hip screws, IT=InterTan Nail, GN=gamma nail, PFNA= proximal femoral nail antirotation

Figure 4 Contribution plot of studies included in this network meta-analysis.

Note: SHS= sliding hip screws, IT=InterTan Nail, GN=gamma nail, PFNA= proximal femoral nail antirotation

Figure 5 Inconsistency test for direct and indirect comparisons.

Note: SHS= sliding hip screws, IT=InterTan Nail, GN=gamma nail, PFNA= proximal femoral nail antirotation

Figure 6 Funnel plots assessment of publication bias of all included studies.

Note: SHS= sliding hip screws, IT=InterTan Nail, GN=gamma nail, PFNA= proximal femoral nail antirotation

Figure 7 Treatments compared with each other in total complications.

Note: SHS= sliding hip screws, IT=InterTan Nail, GN=gamma nail, PFNA= proximal femoral nail antirotation, **CI = confidence interval, PrI = predictive interval**

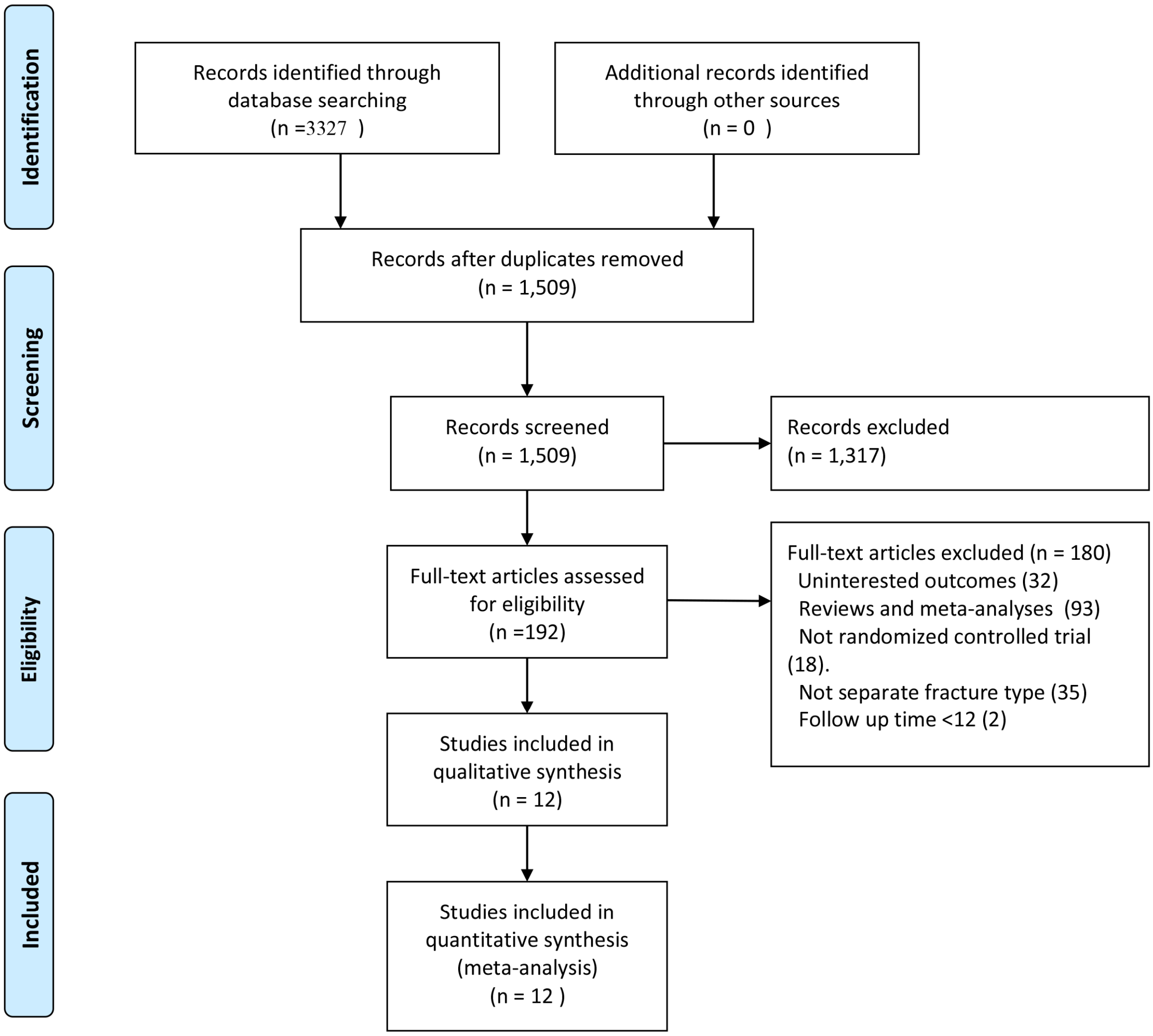
.Figure 8 Surface under the cumulative ranking curve for complication.

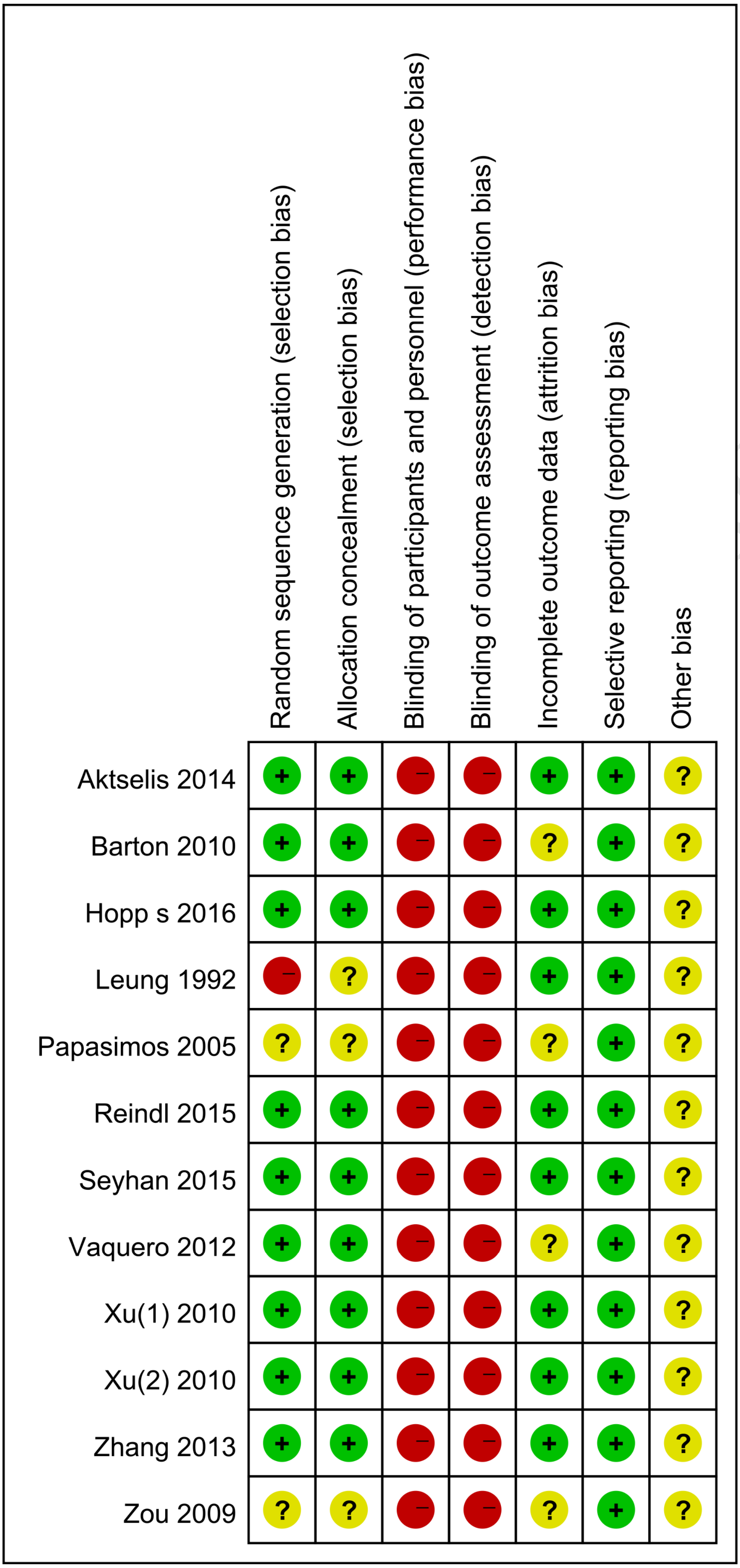
Note: SHS= sliding hip screws, IT=InterTan Nail, GN=gamma nail, PFNA= proximal femoral nail antirotatio

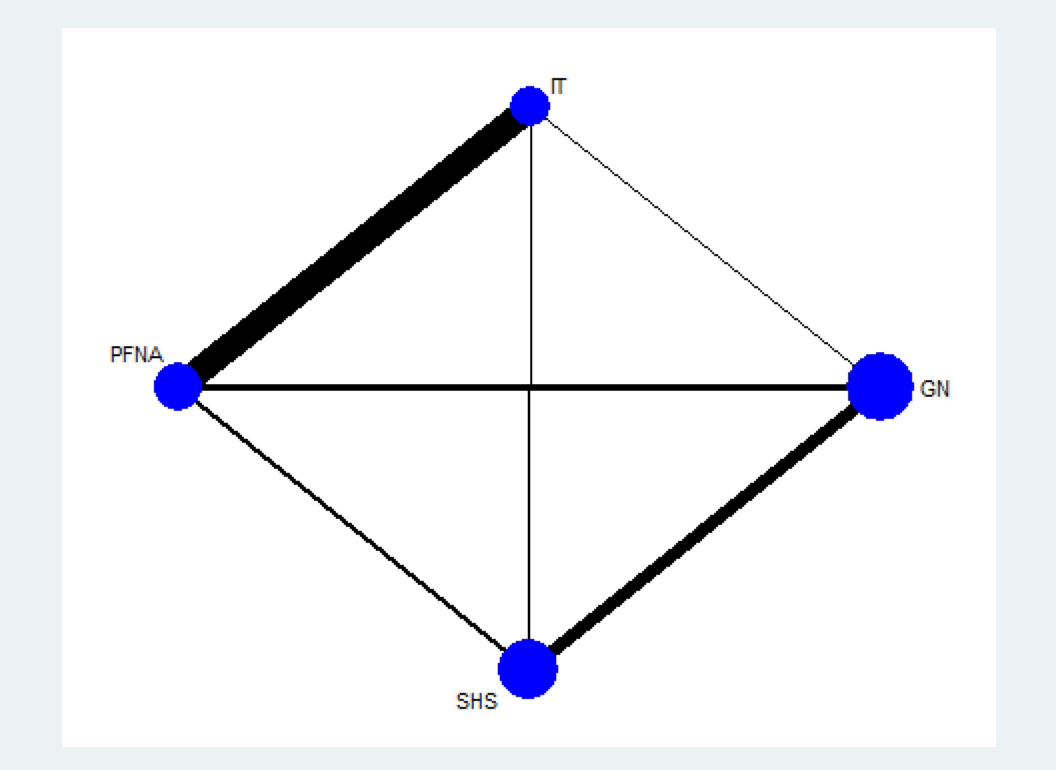
Table 1. Characteristics of the included studies.

study	Design	Country	Intervention		Age(year)		Number of patients		Follow-up term(month)
			I	E	I	E	I	E	
Barton 2010	RCT	UK	GN VS SHS		83.1 (9.5)	83.3 (6.8)	100	110	12
Leung 1992	RCT	HongKong	GN VS SHS		80.8 (8.4)	78.3 (9.5)	63	73	12
Papasimos 2005	RCT	Greece	GN VS SHS		82.8 (NR)	81.4 (NR)	40	40	12
Aktselis 2014	RCT	Greece	GN VS SHS		82.9 (5.8)	83.1 (6.5)	40	40	12
Hopps 2016	RCT	Germany	GN VS IT		80.73 (8.44)	82.70 (7.06)	39	39	20
Zou 2009	RCT	China	PFNA VS SHS		65.0 (13.5)	65 (13.7)	16	11	12
Xu(2) 2010	RCT	China	PFNA VS SHS		78.5 (8.0)	77.9 (7.8)	51	55	12
Zhang 2013	RCT	China	PFNA VS IT		72.4 (8.7)	72.9 (7.6)	56	57	18
Seyhan 2015	RCT	Turkey	PFNA VS IT		75.9 (13.7)	75.3 (13.5)	32	25	24
Reindl 2015	RCT	Canadian	IT and GN VS SHS		82.0 (8.6)	80 (9.9)	48/22	92	12
Vaquero 2012	RCT	Spain	GN VS PFNA		83．5（7．4）	83．6（7．5）	31	33	12
Xu(1) 2010	RCT	China	GN VS PFNA		75.4 (1.0)	76.0 (1.2)	70	66	17

RCT = Randomized Clinical Trial, GN =Gamma nail , PFNA = Proximal femoral nail antirotation, SHS= Sliding hip screws, IT=InterTan Nail, NR= Not reported.

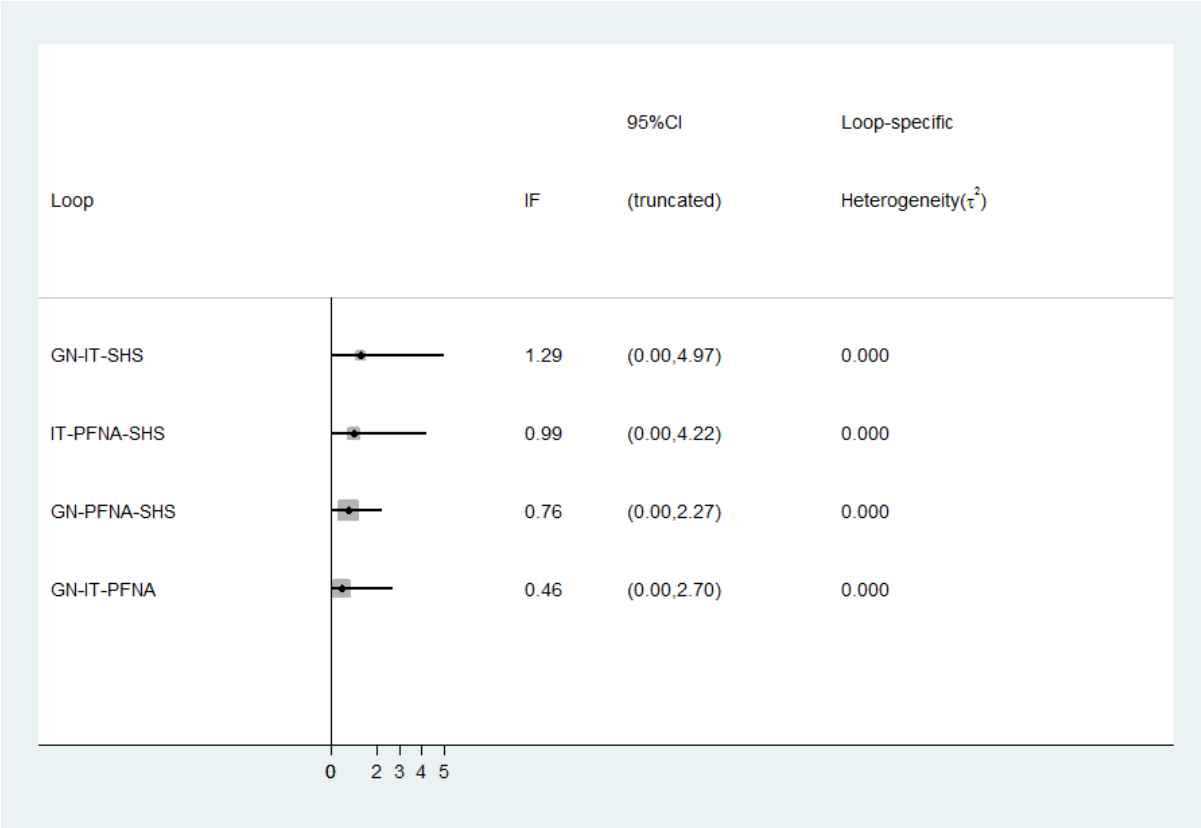

Identification
Screening
Eligibility
Included
Records identified through database searching (n =3327)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 1,509)
Records screened (n = 1,509)
Records excluded (n = 1,317)
Full-text articles assessed for eligibility (n =192)
Full-text articles excluded (n = 180)
Uninterested outcomes (32)
Reviews and meta-analyses (93)
Not randomized controlled trial (18).
Not separate fracture type (35)
Follow up time <12 (2)
Studies included in qualitative synthesis (n = 12)
Studies included in quantitative synthesis (meta-analysis) (n = 12)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Aktselis 2014
Barton 2010
Hopp s 2016
Leung 1992
Papasimos 2005
Reindl 2015
Seyhan 2015
Vaquero 2012
Xu(1) 2010
Xu(2) 2010
Zhang 2013
Zou 2009

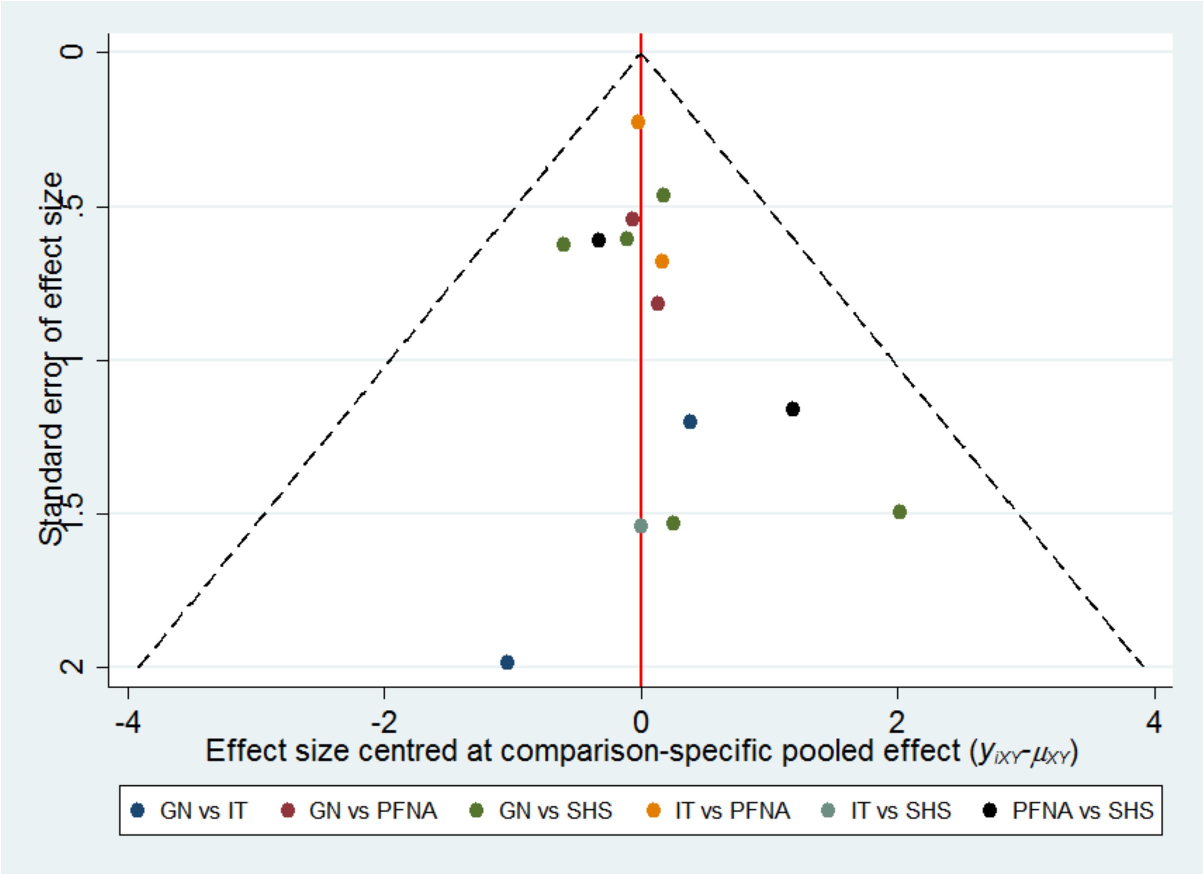

IT
PFNA
GN
SHS

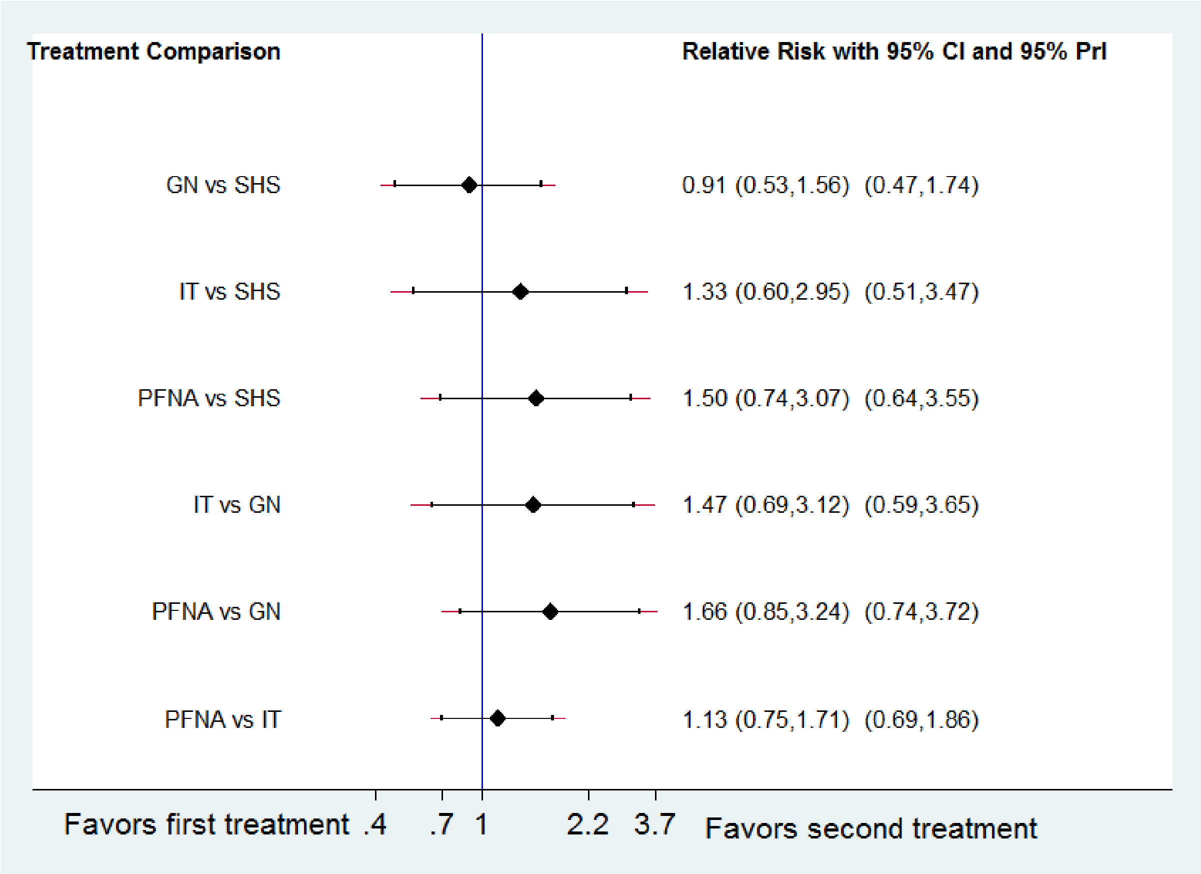
Direct comparisons in the network

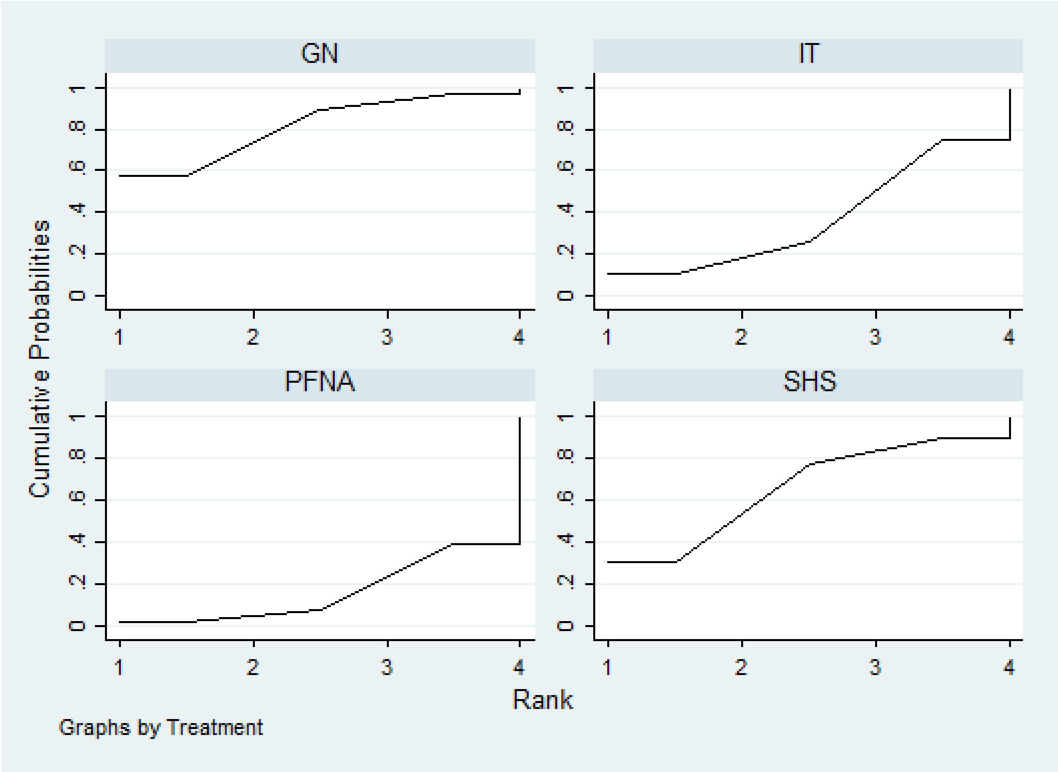
Network meta-analysis estimates	GN vs IT	GN vs PFNA	GN vs SHS	IT vs PFNA	IT vs SHS	PNNA vs SHS
Mixed estimates						
GN vs IT	7.3	28.7	12.7	38.6	2.7	10.0
GN vs PFNA	8.1	44.1	18.4	10.9	2.9	15.6
GN vs SHS	2.0	10.4	75.1		2.1	10.4
IT vs PFNA	3.4	3.4		90.3	1.5	1.5
IT vs SHS	5.3	19.7	25.0	33.2	3.3	13.5
PFNA vs SHS	5.2	28.9	34.1	8.9	3.7	19.3
Indirect estimates						
Entire network	5.5	23.9	26.3	29.0	2.9	12.5
Included studies	2	2	5	2	1	2



Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
GN-IT-SHS 1.29 (0.00,4.97) 0.000
IT-PFNA-SHS 0.99 (0.00,4.22) 0.000
GN-PFNA-SHS 0.76 (0.00,2.27) 0.000
GN-IT-PFNA 0.46 (0.00,2.70) 0.000
0
2
3
4
5


0
.5
1
1.5
2
Standard error of effect size
-4
-2
0
2
4
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
GN vs IT
GN vs PFNA
GN vs SHS
IT vs PFNA
IT vs SHS
PFNA vs SHS


Treatment Comparison
Relative Risk with 95% CI and 95% PrI
GN vs SHS
0.91 (0.53,1.56) (0.47,1.74)
IT vs SHS
1.33 (0.60,2.95) (0.51,3.47)
PFNA vs SHS
1.50 (0.74,3.07) (0.64,3.55)
IT vs GN
1.47 (0.69,3.12) (0.59,3.65)
PFNA vs GN
1.66 (0.85,3.24) (0.74,3.72)
PFNA vs IT
1.13 (0.75,1.71) (0.69,1.86)
Favors first treatment
.4
.7
1
2.2
3.7
Favors second treatment


GN
IT
PFNA
SHS
Cumulative Probabilities
0
.2
.4
.6
.8
1
1
2
3
4
Rank
Graphs by Treatment

Highlights

- The optimal internal fixation device for unstable intertrochanteric fracture remains controversial.
- This is the first article that assesses four different treatments of unstable intertrochanteric fracture using network meta-analysis.
- Network meta-analysis can be used to compare multiple interventions even if there are no head-to-head comparisons.

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

We have no conflicts of interest

Please state any sources of funding for your research

We did not receive any sources of funding.

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

This article does not contain any studies with human participants or animals performed by any of the authors.

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This is a systematic review and meta-analysis. UIN for my research is CRD42018104764
https://www.crd.york.ac.uk/PROSPERO/

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Wu-Bin Shu and Guan-Hua Lan designed the research; Wu-Bin Shu, Xiao-bo Zhang and He-Hui Wang conducted the research;
Xiao-bo Zhang and Hua-ya Lu analyzed data; Wu-Bin Shu and Guan-Hua Lan wrote the draft; all authors read, reviewed and approved the final manuscript. Wu-Bin Shu and Guan-Hua Lan had primary responsibility for final content.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Wu-Bin Shu, Xiao-bo Zhang, Hua-ya Lu, He-Hui Wang, Guan-Hua Lan

Data statement

Our data from the published papers. Two authors independently extracted the data, and differences were resolved through discussion with a third author.