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Original Article

Is proximal femoral nail antirotation superior to gamma nail and dynamic hip screw in treatment of intertrochanteric fractures? a pairwise and network meta-analysis

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Abstract: Purposes: Proximal femoral nail antirotation (PFNA) was theoretically designed to be an ideal intramedullary device for the fixation of intertrochanteric fractures by providing angular and rotational stability. We investigated when compared with Gamma nail (GN) and dynamic hip screw (DHS) whether PFNA was associated with (1) a lower incidence of reoperation, mortality and fixation failures, (2) a lower risk of major complications (wound infection and thromboembolism), (3) less operative blood loss, shorter surgical time, operative fluoroscopy time and hospital stay. Methods: We conducted a comprehensive search in MEDLINE®, EMBASE, OVID and Cochrane Central Register of Controlled Trials and identified 753 papers. Of these, identified 13 randomized controlled trials comparing two (or more) common internal fixation devices (among PFNA, GN and DHS) in treatment of Intertrochanteric fractures. We performed both traditional direct-comparison meta-analysis and network meta-analysis. The strength of evidence was evaluated by using GRADE profiler software. Results: Direct-comparison meta-analysis demonstrated PFNA was associated with less operative blood loss when compared with GN (95% CI, -93.56 to -5.44, low confidence evidence) and DHS (95% CI, -291.90 to -151.58, low confidence evidence), and less operative fluoroscopy time when compared with GN (95% CI, -56.21 to -3.79, low confidence evidence). Network meta-analysis only found that PFNA was associated with less operative blood loss when compared with DHS (95% CI, -342.12 to -81.94) with very low confidence evidence. Conclusions: Current published evidence does not support the superiority of PFNA to other fixation strategies for intertrochanteric fractures. Although use of PFNA may be advantageous in reducing the operative blood loss and fluoroscopy time when compared with GN and DHS, the conclusion was limited and unacceptable because of the relatively low quality of evidences with either low or very low strength of confidence.

Keywords: Intertrochanteric fractures, proximal femoral nail antirotation, Gamma nail, dynamic hip screw, network meta-analysis

Introduction

Fractures of the proximal femur and hip are relatively common source of morbidity and mortality in the elderly. The number of proximal femoral fractures has increased significantly during last decades due to the rising age of the population [1-3]. Intertrochanteric fractures account for approximately 47% of all proximal femoral fractures [4, 5]. However, which is the optimal implant for the fixation of intertrochanteric fractures remain to be a considerable debate. Commonly used devices for treating intertrochanteric fractures include extramedullary fixation such as dynamic hip screw (DHS) and intramedullary fixation such as Gamma nail (GN) for last decades. Proximal femoral nail antirotation (PFNA) is an intramedullary device designed with a helical blade rather than a screw, and is expected to provide better angular and rotational stability, and reduce the implant-related complications [6, 7].

One recent systematic review and meta-analysis [8] compared a series of clinical indicators across PFNA, GN and DHS, determining that PFNA should be a priority choice for treatment of intertrochanteric fractures with minimal rate

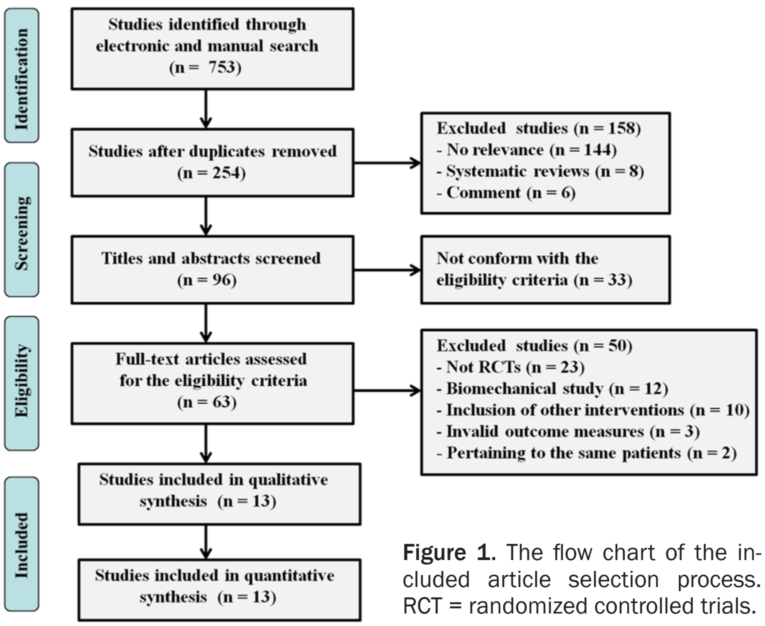


Figure 1. The flow chart of the included article selection process. RCT = randomized controlled trials.

of fixation failure, less blood loss and shorter length of hospital stay. However, the traditional meta-analyses can evaluate only the relative efficacy of two treatments at a time. The scarcity and the low quality of relevant RCT literatures also limited performing a direct meta-analysis and made the conclusions less reliable. Unlike the traditional meta-analysis, network meta-analysis permits simultaneous comparison of no less than 3 interventions. Using a Bayesian evidence analysis, all indirect comparison could be taken into account to arrive at a single, integrated estimate of effect of all included treatments based on all the available evidences [9].

We therefore conducted a network meta-analysis of randomized controlled trials to determine whether (1) PFNA was superior to GN and DHS for intertrochanteric fractures with a lower incidence of reoperation, mortality and fixation failures; (2) PFNA was associated with a lower incidence of major complications (wound infection and thromboembolism); (3) PFNA could reduce the operative blood loss, the length of surgical time, fluoroscopy time and hospital stay. In order to access the strength of evidence, we also use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach [10, 11] for all the pooled clinical outcomes.

Materials and methods

Search strategy and eligibility criteria

Our systematic review was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12]. Through an electronic search and independent, manual searches by two clinical librarians (S. Yin and X. Dai), we identified all RCTs in all languages up to Oct 2015 that met the following eligibility criteria: (1) the study enrolled adult patients with intertrochanteric fractures; (2) use of random allocations of treatments; (3) inclusion of at least two inventions among PFNA, GN and DHS; (4) inclusion of at least one valid primary outcomes. The primary outcomes included: (1) reoperation; (2) mortality; (3) fixation failures; (4) wound infection; (5) thromboembolism; (6) operative blood loss; (7) the length of surgical time; (8) operative fluoroscopy time; (9) the length of hospital stay. The secondary outcomes included: (1) functional outcomes, such as pain assessment measured by VAS or the numerical rating scale, Harris hip score, SF-36 mental and physical health surveys, EuroQol 5D score, walking ability score; (2) fracture healing time; (3) patient satisfaction. The sources of electronic searching include MEDLINE®, EMBASE, OVID, Google Scholar and The Cochrane Central Register of Controlled Trials. The following key terms were included in our searches: (*intertrochanteric fractures* OR *peritrochanteric fractures* OR *extracapsular hip fractures* OR *trochanteric fractures*) AND (*PFNA* OR *proximal femoral nail antirotation* OR *proximal femoral nail* OR *DHS* OR *dynamic hip screw* OR *Gamma nail* OR *trochanter fixation nail* OR *intramedullary nail*). In addition, bibliographies of all selected full text articles were reviewed to identify additional articles.

Study selection

After applying the search strings, we identified 753 potentially eligible articles. Two reviewers

Table 1. Characteristics of included studies

Study	Design	Interventions Compared and sample size			Mean Age (years)	Follow-up (months)	Outcomes	Country
		PFNA	DHS	GN				
Adams 2001 [13]	Single RCT		197	203	81	12	1, 3-7, 10	UK
Bridle 1991 [14]	Single RCT		51	49	81.9	6	2-5, 10	UK
Butt 1995 [15]	Single RCT		48	47	78.5	NA	2-5	UK
Garg 2011 [16]	Single RCT	42	39		62.2	40	2-3, 10	India
Leung 1992 [17]	Single RCT		113	113	79.6	7.2	2-9	HK, China
O'Brien 1995 [18]	Single RCT		49	53	80.1	13	1-5	UK
Radford 1993 [19]	Single RCT		100	100	80.5	12	2-5	UK
Vaquero 2012 [20]	Multicentre RCT	31		30	85	12	3, 4, 6, 8, 10	Spain
Verettas 2010 [21]	Single RCT		60	60	80.1	NA	2, 4, 5, 10	Greece
Xu 2010 [22]	Single RCT	51	55		78.2	12	1-10	China
Yaozeng 2010 [23]	Single RCT	55		52	76.7	17.5	1, 3, 4, 6-10	China
Zehir 2014 [24]	Single RCT	96	102		77	16	2-10	Turkey
Zou 2009 [25]	Single RCT	58	63		65	12	1, 3-7, 9, 10	China

Outcomes: 1. Reoperation; 2. Mortality; 3. Fixation failures; 4. Wound infection; 5. Thromboembolism; 6. Length of surgical time; 7. Operative blood loss; 8. Length of hospital stay; 9. Fluoroscopy time; 10. Functional outcome.

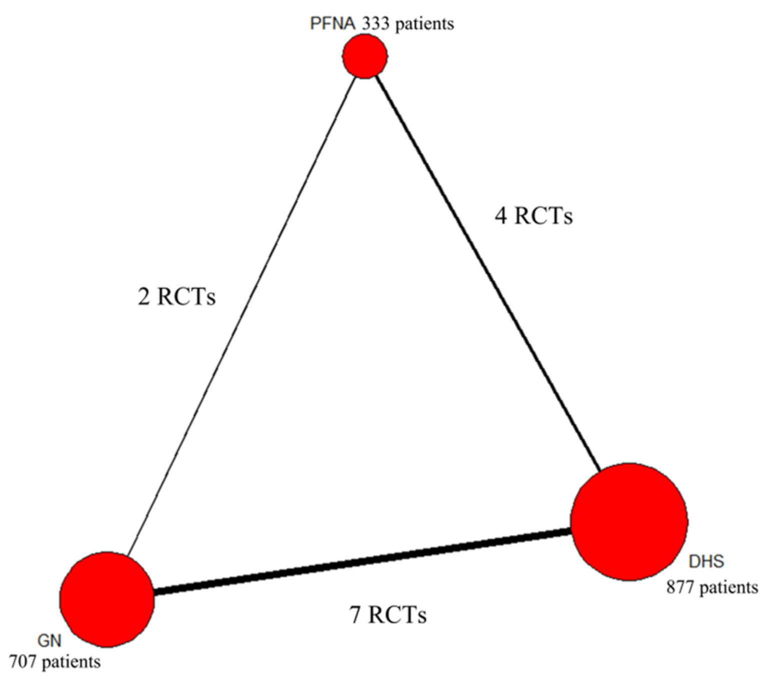


Figure 2. Network evidence of included studies. The size of red circles represent the total patients number of each invention, whereas the thickness of solid lines represent the number of trials comparing the connected inventions. PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails, RCT = randomized controlled trials.

(S. Yin and D. Zhang) independently checked the titles and abstracts of all articles. Of the 753 articles, 499 were duplicates (**Figure 1**). One hundred and forty-four articles were excluded based on their titles and abstracts with apparent lack of relevance. Another fourteen systematic review articles or comments were also excluded. Of the remaining 96 articles, sixty-three proved potentially eligible for our survey. The full texts of potentially eligible articles were assessed by the same two reviewers. If no agreement could be reached, a third reviewer (H. Du) made the final decision. Of these, 50 were excluded for not randomized trials, biomechanical studies, invalid outcome measures, inclusion of other interventions, or pertaining to the same patients. Thirteen eligible trials [13-25] involving a total of 1917 patients treated for intertrochanteric fractures were eventually identified in the current review and meta-analysis. Full-text, published articles and unpublished data of completed studies were included.

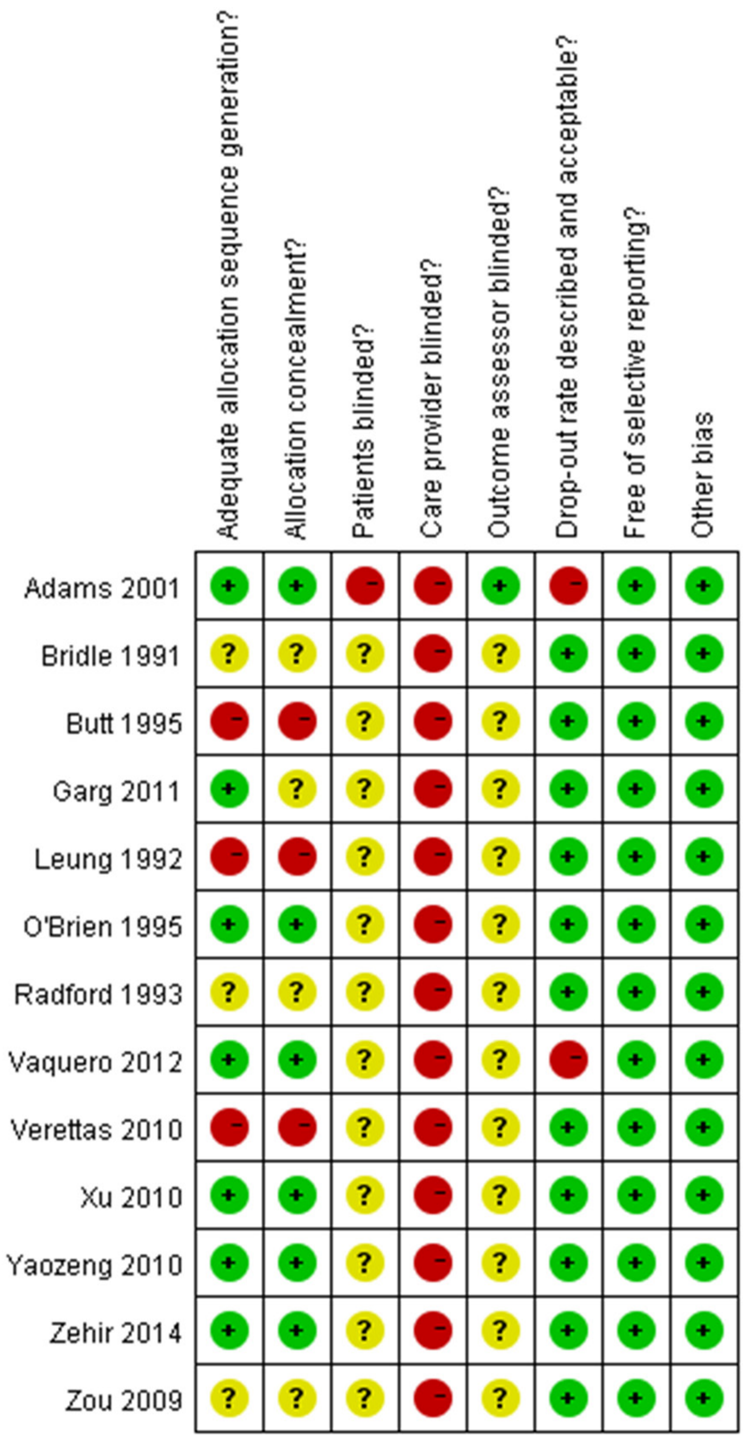


Figure 3. The risk of bias for the included studies.

We recorded the characteristics of the 13 included papers and details of the clinical outcome measurement (**Table 1**). All included studies were published in English with definite inclusion and exclusion criteria. The mean follow-up period ranged from 6 to 40 months. The mean age of the patients at the time of surgery ranged from 65 to 85 years. The included 13 articles contained three direct comparisons: four PFNA versus DHS [16, 22, 24, 25], two PFNA versus GN [20, 23], and seven DHS versus GN [13-15, 17-19, 21]. The network evidence of these trials is summarized in **Figure 2**.

Methodological quality assessment

The risk of bias was independently assessed by two reviewers (S. Yin and D. Zhang) using the modified criteria recommended by the Cochrane Back Review Group (updated March 2011) [26, 27]. The reviewers tried to reach consensus on each criteria. Based on the recommendation by the Cochrane Back Review Group, studies were rated as having "low risks of bias" when at least four of the 8 criteria were met without serious flaws. Studies with serious flaws or those in which fewer than four of the criteria were met were rated as having "high risks of bias." Among all the included articles, 7 were considered to meet at least four of the 8 criteria, without serious flaws, and were rated as "low risk of bias" (**Figure 3**). The remaining six trials were graded as "high risk of bias", because fewer than four of the criteria were met in these studies. Seven articles reported adequate allocation sequences, and six articles reported adequate allocation concealments. Only one trial blinded outcome assessors, and two trials had significant patient loss to follow-up.

Table 2. Strength of evidence for pooled data of direct-comparison meta-analysis

Outcome	Comparison	Studies (n)	Strength of evidence	Summary
Reoperation	PFNA versus DHS	2	Low ++○○	No statistical difference
	PFNA versus GN	1	Low +○○○	No statistical difference
	DHS versus GN	2	Moderate +++○	No statistical difference
Mortality	PFNA versus DHS	3	Moderate +++○	No statistical difference
	DHS versus GN	6	Moderate +++○	No statistical difference
Fixation failures	PFNA versus DHS	4	Low +○○○	No statistical difference
	PFNA versus GN	2	Low ++○○	No statistical difference
	DHS versus GN	6	Moderate +++○	No statistical difference
Wound infection	PFNA versus DHS	3	Low ++○○	No statistical difference
	PFNA versus GN	2	Very low +○○○	No statistical difference
	DHS versus GN	7	Moderate ++○○	No statistical difference
Thromboembolism	PFNA versus DHS	2	Low ++○○	No statistical difference
	DHS versus GN	6	Moderate +++○	No statistical difference
Length of surgical time	PFNA versus DHS	3	Low +○○○	No statistical difference
	PFNA versus GN	2	Low +○○○	No statistical difference
	DHS versus GN	2	Low +○○○	GN is superior to DHS
Operative blood loss	PFNA versus DHS	3	Low +○○○	PFNA is superior to DHS
	PFNA versus GN	1	Low ++○○	PFNA is superior to GN
	DHS versus GN	2	Very low +○○○	No statistical difference
Length of hospital stay	PFNA versus DHS	2	Moderate ++○○	No statistical difference
	PFNA versus GN	2	Moderate +++○	No statistical difference
	DHS versus GN	1	Low ++○○	No statistical difference
Fluoroscopy time	PFNA versus DHS	3	Very low +○○○	No statistical difference
	PFNA versus GN	1	Low ++○○	PFNA is superior to GN
	DHS versus GN	1	Very low ++○○	GN is superior to DHS

Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

Table 3. Strength of evidence for pooled data of network meta-analysis

Outcome	Studies (n)	Strength of evidence	Summary
Reoperation	5	Low ++○○	No statistical difference in outcome
Mortality	9	Low ++○○	No statistical difference in outcome
Fixation failures	12	Moderate +○○○	No statistical difference in outcome
Wound infection	12	Very low +○○○	No statistical difference in outcome
Thromboembolism	8	Low ++○○	No statistical difference in outcome
Length of surgical time	7	Low +○○○	No statistical difference in outcome
Operative blood loss	6	Very low +○○○	PFNA is superior to DHS
Length of hospital stay	5	Low ++○○	No statistical difference in outcome
Fluoroscopy time	5	Very low +○○○	No statistical difference in outcome

Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws.

Two reviewers (S. Yin and D. Zhang) independently evaluated the heterogeneity of the included studies. For direct comparisons, the heterogeneity was assessed using the chi-square test [28]. The value of I^2 as 25%, 50%, and 75% indicated low, moderate, and high inconsistency, respectively. When I^2 was greater than 50%, we tried to perform a sensitivity analysis for the measured effects by omitting the study which may have largely influenced the clinical findings. For network meta-analysis, we evaluated if there was no difference between

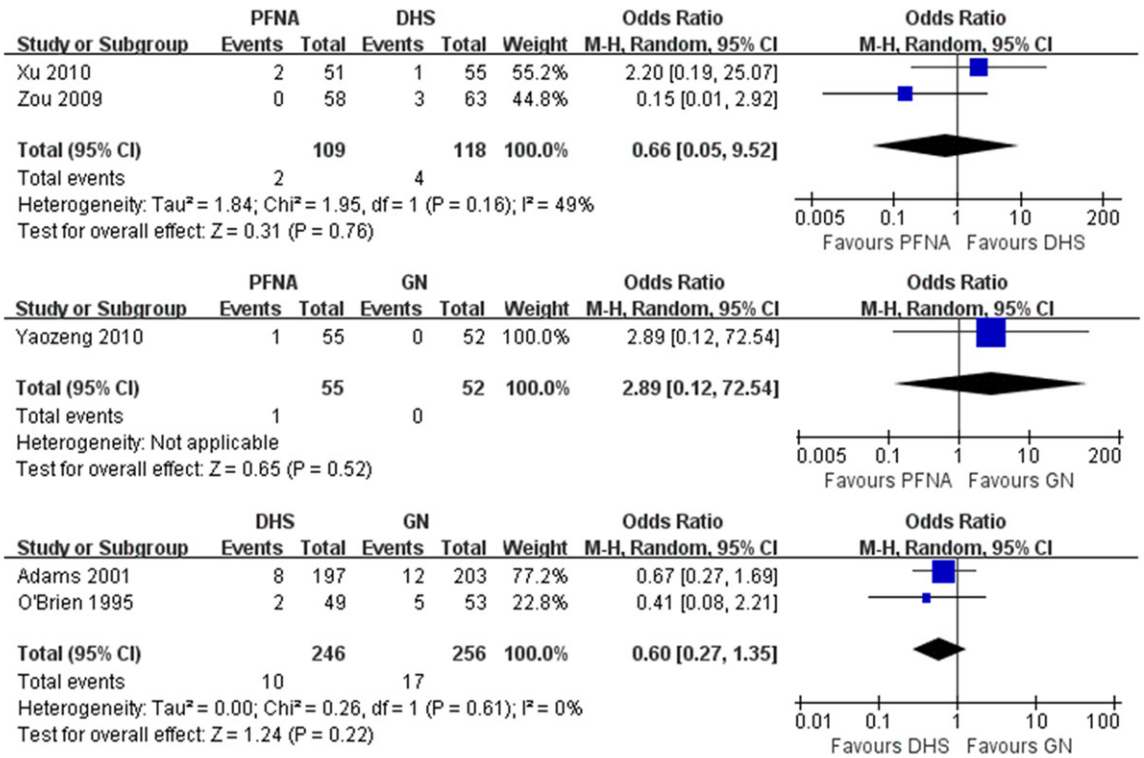


Figure 4. The forest plots of pair-wised meta-analysis comparing the rates of reoperation of the three implants. M-H = Mantel-Haenszel, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

Table 4. Odd radios of reoperation for direct-comparison meta-analysis and network meta-analysis

PFNA	2.60 (0.13-11.27)	4.08 (0.11-19.57)
0.66 (0.05-9.52)	DHS	1.912 (0.21-6.36)
2.89 (0.12-72.54)	0.60 (0.27-1.35)	GN

Odd radios (ORs) of reoperation lower than 1 favor the column-defining treatment. ORs in lower left of the table represented the results of direct-comparison meta-analysis, and the upper right of the table represented the results of network meta-analysis. Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

direct and indirect estimates generated by using a node-splitting procedure with 95% CI.

Data and statistical analysis

For direct comparisons, the Mantel-Haenszel statistical method with the random effects method was used for dichotomous outcomes, and odds ratios (ORs) were calculated. For continuous outcomes the statistical inverse variance method was used with the random effects analysis model, and mean differences (MDs) were calculated. Both outcomes were calculated with corresponding 95% CIs. We used Review Manager software (RevMan Version 5.1.6, The Cochrane Collaboration, Copenhagen, Denmark) for statistical analysis of direct comparisons. For indirect comparisons, a network meta-analysis was conducted using WinBUGS software (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) and R software GeMTC package (version 2.15.2; http://www.R-project.org) with random effects chaimani models. We also calculated the probability of treatment ranking using surface under cumulative ranking curve (SUCRA) method for each parameter [29]. A higher SUCRA value suggests better results for respective treatment method.

We rated the strength of evidence for all the pooled clinical outcomes by using the GRADE profiler software (GRADEpro, Version 3.6, The Cochrane Collaboration, Copenhagen, Denmark) [10, 11], a rating system with four levels of evidence (high, moderate, low, and very low), taken from the Cochrane Back Review Group.

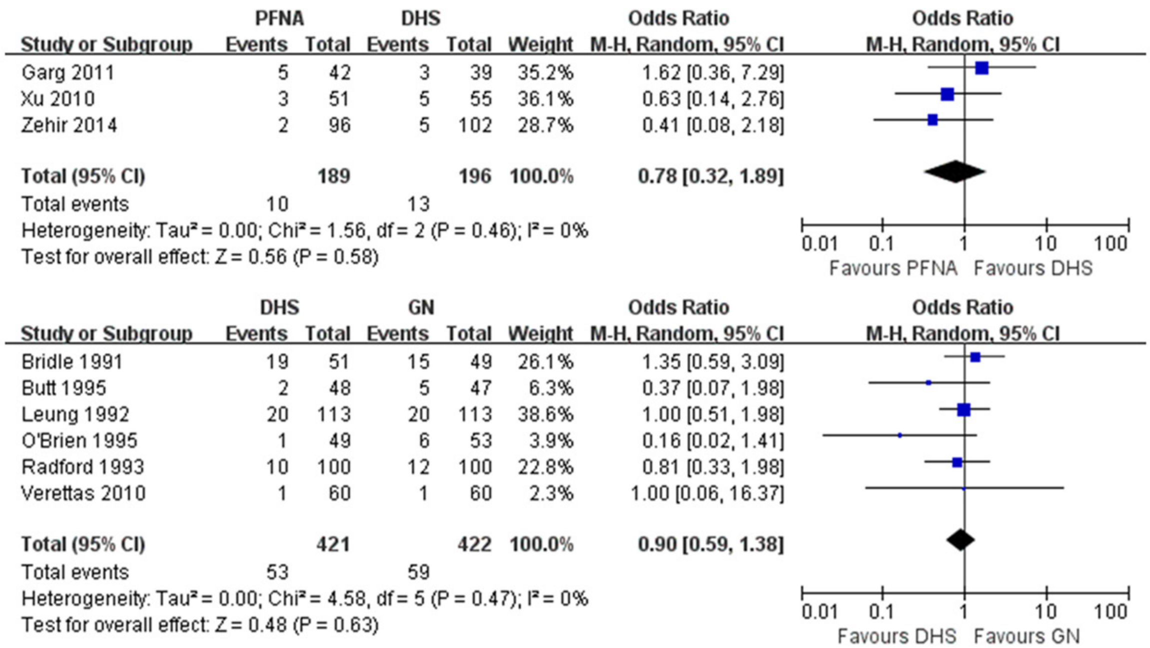


Figure 5. The forest plots of pair-wised meta-analysis comparing the rates of mortality across the three implants. M-H = Mantel-Haenszel, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

Table 5. Odd radios of mortality for direct-comparison meta-analysis and network meta-analysis

PFNA	1.57 (0.46-3.91)	2.13 (0.50-6.32)
0.78 (0.32-1.89)	DHS	1.35 (0.70-2.62)
-	0.90 (0.59-1.38)	GN

Odd radios (ORs) of mortality lower than 1 favor the column-defining treatment. ORs in lower left of the table represented the results of direct-comparison meta-analysis, and the upper right of the table represented the results of network meta-analysis. Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hipscrews, GN = Gamma nails.

Study design, risk for bias, consistency, directness, and precision were assessed for rating the strength of evidence. The strength of evidence was rated for all the pooled direct and indirect results in our analysis. Owning to the high risk of bias and poor precision of the included trials, no high-quality evidence was obtained in our study. For direct comparisons, of all 25 possible comparisons there were a total of eight moderate quality evidences for reoperation (DHS versus GN), mortality (PFNA versus DHS, and DHS versus GN), fixation failures (DHS versus GN), wound infection (DHS versus GN), thromboembolism (DHS versus GN), length of hospital stay (PFNA versus DHS, and PFNA versus GN) (**Table 2**). For indirect comparisons, there was only one moderate quality evidence for fixation failures (**Table 3**). The rest pooled results for both direct and indirect comparisons were all low or very low confidence evidences.

Results

Direct-comparison meta-analysis

A total of five trials reported triangular direct comparisons for reoperation across PFNA, DHS and GN. No differences were observed with direct comparisons across the three devices (**Figure 4**; **Table 4**). There were no heterogeneities with the triangular comparisons. Similarly, for mortality, two possible pair-wise meta-analysis was performed for 3 RCTs comparing PFNA versus DHS and 6 RCTs comparing DHS versus GN. No differences were found with two comparisons and no heterogeneity was observed (**Figure 5**; **Table 5**). For fixation failures, another triangular direct comparison was conducted with a total of 12 trials and there was no difference across the three fixation methods (**Figure 6**; **Table 6**). However, a moderate heterogeneity (P = 0.09; I^2 = 54%) was found in fixation failures between PFNA and DHS. After a sensitivity analysis by omitting the study from Garg et al. [16], no heterogeneity was found among stud-

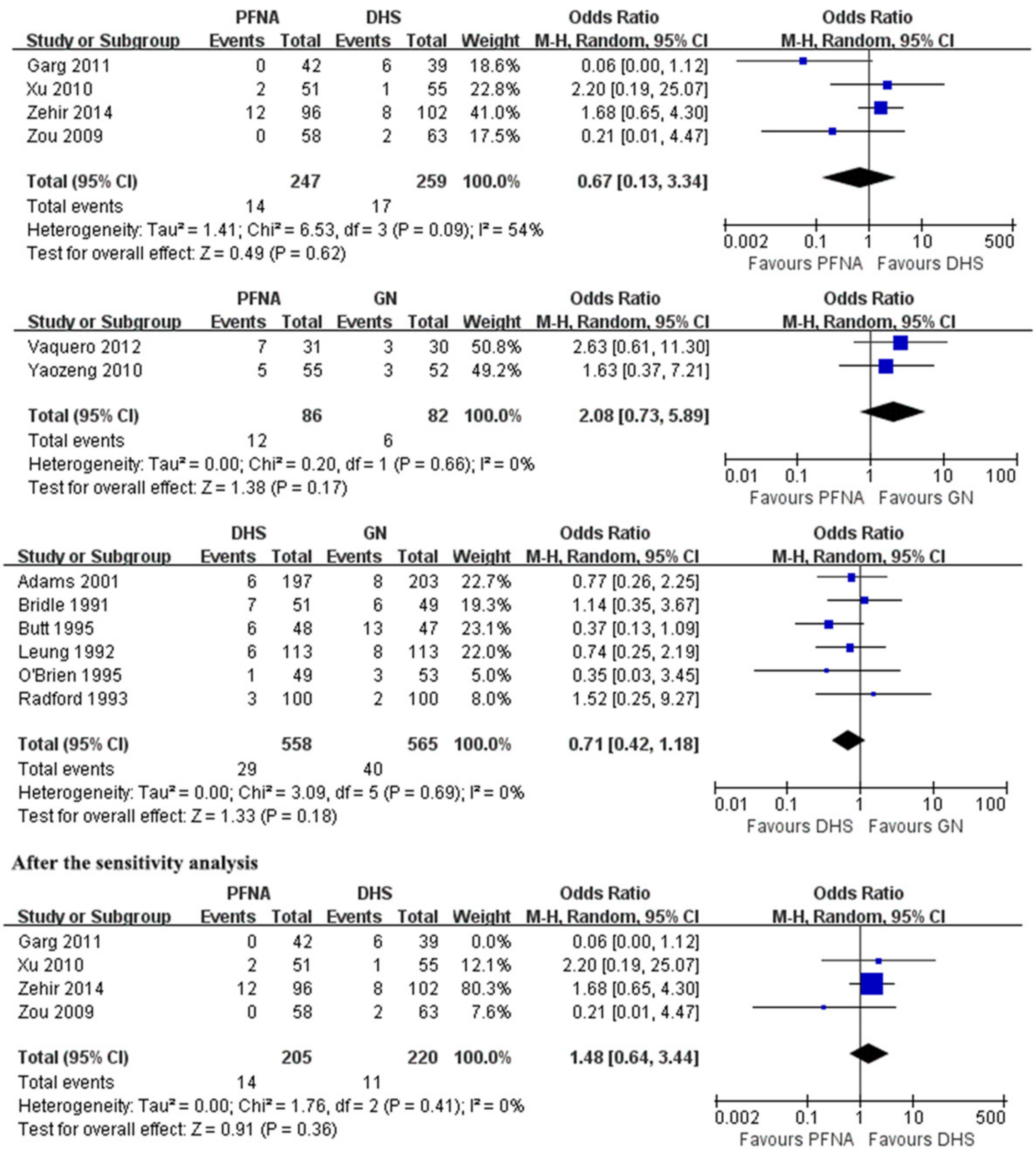


Figure 6. The forest plots of pair-wised meta-analysis comparing fixation failures across the three implants before and after the sensitivity analysis. M-H = Mantel-Haenszel, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

ies (P = 0.41; I^2 = 0%) and no difference was observed with PFNA and DHS comparison (OR 1.48; 95% CI = 0.64 to 3.44; P = 0.36).

For major complications, twelve trials and eight trials reported direct comparisons of wound infection and thromboembolism across PFNA, DHS and GN, respectively. Pair-wise meta-analyses showed no difference in wound infection and thromboembolism across the three devices (**Figures 7** and **8**). There was a moderate heterogeneity (P = 0.09; I^2 = 65%) in wound infection between PFNA and GN. Because of small number of studies, a sensitivity analysis could not be performed for the measured effects.

Table 6. Odd radios of fixation failures for direct-comparison meta-analysis and network meta-analysis

PFNA	0.98 (0.39-2.18)	1.13 (0.40-2.60)
1.48 (0.64-3.44)	DHS	1.21 (0.56-2.26)
2. 08 (0.73-5.89)	0.71 (0.42-1.18)	GN

Odd radios (ORs) of fixation failures lower than 1 favor the column-defining treatment. ORs in lower left of the table represented the results of direct-comparison meta-analysis, and the upper right of the table represented the results of network meta-analysis. Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

The possible direct-comparison meta-analysis demonstrated that PFNA was associated with less operative blood loss when compared with GN (MD = -49.50, 95% CI, -93.56 to -5.44; P = 0.03) and DHS (MD = -221.74, 95% CI, -291.90 to -151.58; P < 0.00001) with both low confidence evidences (**Figure 9**; **Table 7**). For length of surgical time, we found that GN was associated with shorter surgical time comparing with DHS (MD = 9.51, 95% CI, 2.86 to 16.15; P = 0.005; low confidence evidence), and no superiority of PFNA to DHS and GN was observed (**Figure 10**; **Table 8**). There were no differences in length of hospital stay among the triangular comparisons (**Figure 11**). For operative fluoroscopy time, only one randomized trial reported that PFNA was superior to GN with less fluoroscopy time (MD = -30.00, 95% CI, -56.21 to -3.79; P = 0.02; low confidence evidence) (**Figure 12**; **Table 9**). For most of the continuous outcomes pooled from direct-comparison meta-analyses mentioned above, we found high inconsistencies with I^2 greater than 75%. Owning to the small number of included studies, it was difficult to perform sensitivity analyses to improve the heterogeneities of direct comparisons. However, we rated down the quality of evidence when high heterogeneity was observed on the basis of the GRADE approach.

Network meta-analysis

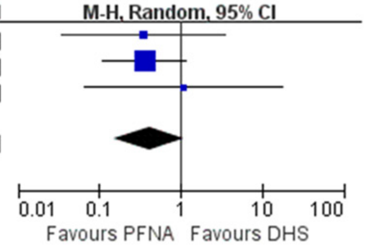
Network meta-analysis only found that PFNA was associated with less operative blood loss when compared with DHS (MD = -208.99, 95% CI, -342.12 to -81.94; P < 0.0001) with very low confidence evidence (**Tables 3** and **7**). SUCRA scores revealed the following probabilities of being the best treatment for operative blood loss: PFNA = 84.8%, DHS = 12.4%, GN = 2.8%. For other parameters, there were no more differences in the incidence of reoperation, mortality, fixation failures, major complications (wound infection and thromboembolism) and operative blood loss, surgical time, fluoroscopy time and hospital stay across PFNA, GN and DHS for treatment of Intertrochanteric fractures (**Table 3**).

Discussion

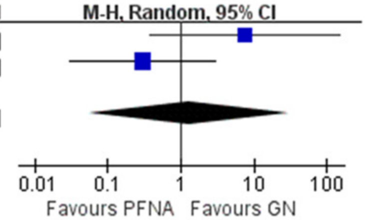
Since the operative treatment of intertrochanteric fractures of the proximal femur was firstly introduced in the 1950s, a number of different designs and devices have been developed by different manufacturers. Surgery for intertrochanteric fractures fracture aims at early recovery, freedom from reoperation and prevention of further complications [30]. Over the last two decades, there has been a great deal of controversy over the optimum treatment and device for fixation of intertrochanteric fractures. One recent systematic review and meta-analysis [8] determined that PFNA should be a priority choice for treatment of intertrochanteric fractures with minimal rate of fixation failure, less blood loss and shorter length of hospital stay when compared with GN and DHS. However, with the scarcity and the low quality of relevant RCT literatures, and without the assessment of the quality of evidence, the conclusions were limited and trustless. The optimal methodological tool for this question is network analysis because it enables pooling of data from both direct and indirect comparisons and increases the power of the tests and reduce type I statistical errors [31]. Therefore we aimed to use both pairwise and network meta-analysis to determine whether PFNA was superior to DHS and GN with lower incidence of reoperation, mortality, fixation failures, major complications, and less operative blood loss, surgical time, operative fluoroscopy time and hospital stay in treatment of intertrochanteric fractures.

Readers should be aware of limitations in the literature in general and our study in particular. First, a majority of the pooled effect estimates from direct and indirect comparisons were graded as either low or very low confidence and no high-quality evidence was obtained in our study. This low grade was mainly driven by the high risk of bias such as lack of blinding, and poor precision of the included trials. Second,

Study or Subgroup	PFNA Events	PFNA Total	DHS Events	DHS Total	Weight	Odds Ratio M-H, Random, 95% CI
Xu 2010	1	51	3	55	18.3%	0.35 [0.03, 3.44]
Zehir 2014	4	96	11	102	69.3%	0.36 [0.11, 1.17]
Zou 2009	1	58	1	63	12.4%	1.09 [0.07, 17.80]
Total (95% CI)		**205**		**220**	**100.0%**	**0.41 [0.15, 1.09]**
Total events	6		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 2 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.78 (P = 0.08)						



Study or Subgroup	PFNA Events	PFNA Total	GN Events	GN Total	Weight	Odds Ratio M-H, Random, 95% CI
Vaquero 2012	3	31	0	30	45.3%	7.49 [0.37, 151.50]
Yaozeng 2010	1	55	3	52	54.7%	0.30 [0.03, 3.00]
Total (95% CI)		**86**		**82**	**100.0%**	**1.30 [0.05, 30.70]**
Total events	4		3			
Heterogeneity: Tau² = 3.40; Chi² = 2.82, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 0.16 (P = 0.87)						



Study or Subgroup	DHS Events	DHS Total	GN Events	GN Total	Weight	Odds Ratio M-H, Random, 95% CI
Adams 2001	6	197	9	203	47.0%	0.68 [0.24, 1.94]
Bridle 1991	2	51	1	49	8.8%	1.96 [0.17, 22.33]
Butt 1995	2	48	2	47	13.0%	0.98 [0.13, 7.25]
Leung 1992	3	113	1	113	10.0%	3.05 [0.31, 29.82]
O'Brien 1995	1	49	0	53	5.0%	3.31 [0.13, 83.17]
Radford 1993	4	100	1	100	10.7%	4.13 [0.45, 37.57]
Verettas 2010	2	60	0	60	5.6%	5.17 [0.24, 110.01]
Total (95% CI)		**618**		**625**	**100.0%**	**1.33 [0.65, 2.74]**
Total events	20		14			
Heterogeneity: Tau² = 0.00; Chi² = 4.39, df = 6 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.44)						

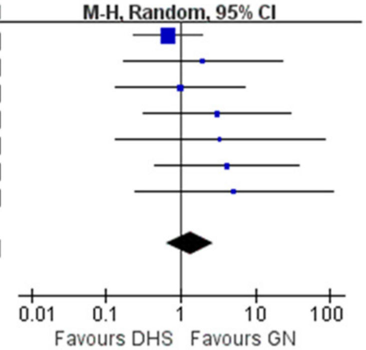
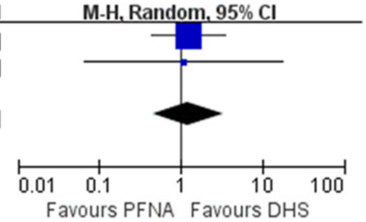


Figure 7. The forest plots of the direct comparison evidence for wound infection across the three implants. M-H = Mantel-Haenszel, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

Study or Subgroup	PFNA Events	PFNA Total	DHS Events	DHS Total	Weight	Odds Ratio M-H, Random, 95% CI
Zehir 2014	8	96	7	102	87.5%	1.23 [0.43, 3.54]
Zou 2009	1	58	1	63	12.5%	1.09 [0.07, 17.80]
Total (95% CI)		**154**		**165**	**100.0%**	**1.21 [0.45, 3.26]**
Total events	9		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						



Study or Subgroup	DHS Events	DHS Total	GN Events	GN Total	Weight	Odds Ratio M-H, Random, 95% CI
Adams 2001	10	197	9	203	43.8%	1.15 [0.46, 2.90]
Bridle 1991	0	51	1	49	3.6%	0.31 [0.01, 7.89]
Butt 1995	3	48	2	47	11.1%	1.50 [0.24, 9.41]
O'Brien 1995	0	49	3	53	4.2%	0.15 [0.01, 2.90]
Radford 1993	6	100	8	100	31.0%	0.73 [0.25, 2.20]
Verettas 2010	1	60	2	60	6.3%	0.49 [0.04, 5.57]
Total (95% CI)		**505**		**512**	**100.0%**	**0.86 [0.46, 1.58]**
Total events	20		25			
Heterogeneity: Tau² = 0.00; Chi² = 2.78, df = 5 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						

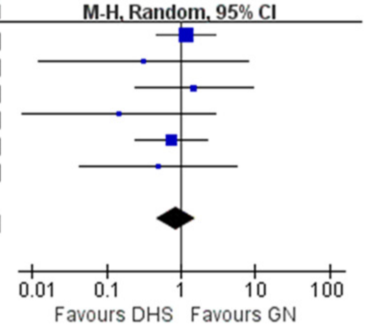


Figure 8. The forest plots of the direct comparison evidence for thromboembolism across the three implants. M-H = Mantel-Haenszel, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

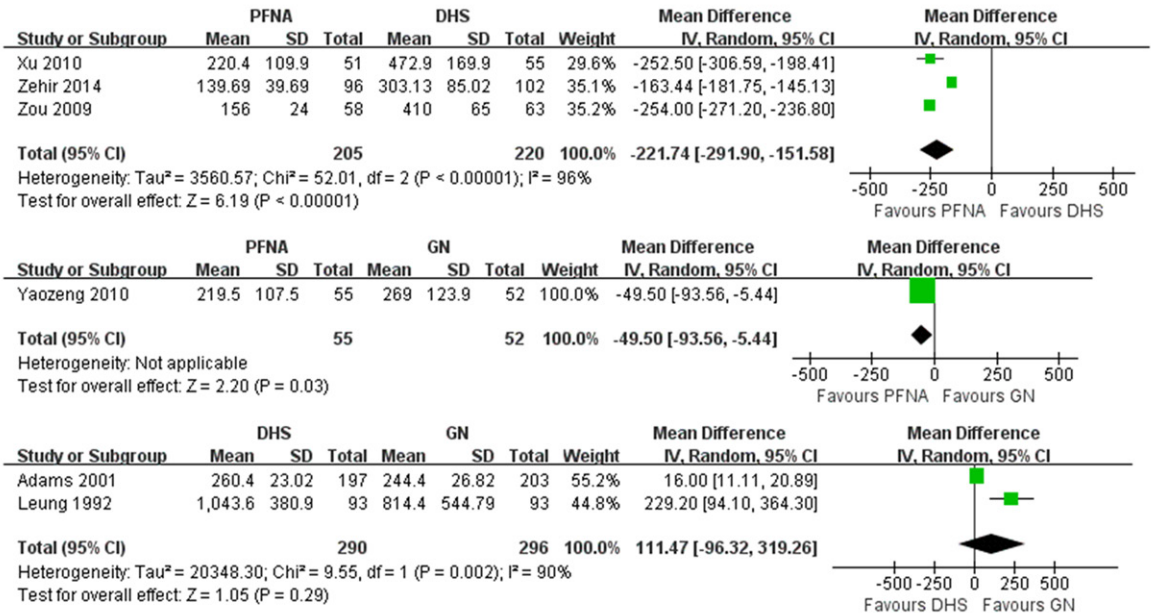


Figure 9. The forest plots of direct comparison evidence for operative blood loss across the three implants. IV = inverse variance, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

Table 7. Mean differences of operative blood loss for direct-comparison meta-analysis and network meta-analysis

PFNA	208.99 (81.94-342.12)	91.25 (-86.24-253.66)
-221.74 (-291.90- -151.58)	DHS	-117.87 (-281.88-25.25)
-49.50 (-93.56- -5.44)	111.47 (-96.32-319.26)	GN

For operative blood loss, mean differences (MDs) lower than 0 favor the column-defining treatment. Direct comparisons were shown in the lower left. Indirect comparisons were shown in the upper right. Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

for most of the continuous effect estimate from direct comparisons, high heterogeneities of included trials with I^2 greater than 75% were observed, that further more rated down the strength of evidence. The main reason for the significant heterogeneities may be the variation in the skills and experiences of the surgeons especially for the newly developed devices. Because of the small number of included studies, it was difficult to perform sensitivity analyses to improve the heterogeneities of direct comparisons. Third, a great part of the included trials had not reported the relationship between clinical outcomes and fracture types, so we could not conduct a sub-analysis on different fracture types such as stable and unstable fractures across the three implants. Finally, due to the method and quantitative differences in function among the treatment options, functional outcomes had not been involved in our research. Our review differs from previously published reviews [8, 32, 33] because it provides an updated synthesis of the available state with both direct and indirect evidences. Furthermore, we assessed the strength of evidence by using the GRADE approach and arrive at a comprehensive conclusion on the optimum treatment for fixation of intertrochanteric fractures.

Our study results suggest that the three commonly used devices in treatment of intertrochanteric fractures perform similarly in most of the clinical outcomes. Both direct-comparison meta-analysis and network meta-analysis demonstrated no differences among PFNA, DHS and GN in the incidence of reoperation, mortality, fixation failures, major complications (wound infection and thromboembolism), oper-

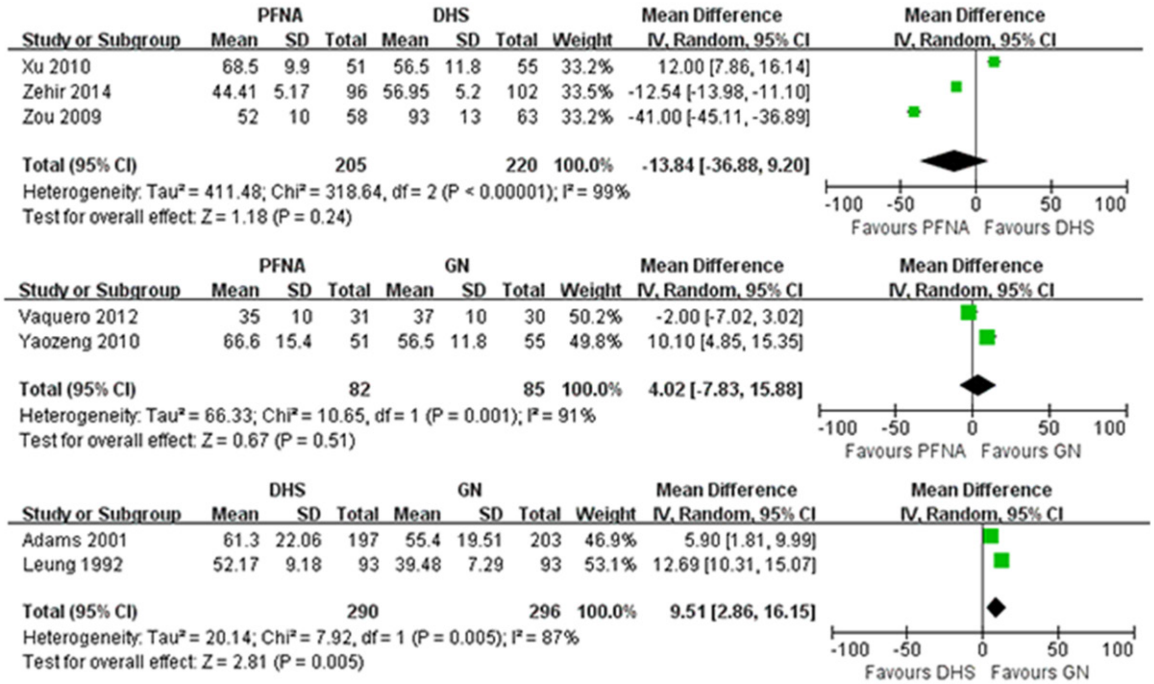


Figure 10. The forest plots of pair-wised meta-analysis comparing length of surgical time across the three implants. IV = inverse variance, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

Table 8. Mean differences of length of surgical time for direct-comparison meta-analysis and network meta-analysis

PFNA	13.82 (-9.32-37.13)	4.37 (-21.16-30.18)
-13.84 (-36.88-9.20)	DHS	-9.54 (-35.23-16.63)
4.02 (-7.83-15.88)	9.51 (2.86-16.15)	GN

For length of surgical time, mean differences (MDs) lower than 0 favor the column-defining treatment. Direct comparisons were shown in the lower left. Indirect comparisons were shown in the upper right. Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

ative blood loss, surgical time, and hospital stay. Although the pooled result showed that use of PFNA may be associated with less operative blood loss (both direct and indirect evidences) and shorter fluoroscopy time (only direct evidence) when compared with GN and DHS, the conclusion was limited and unacceptable because of the relatively low quality of evidences with either low or very low strength of confidence.

With minimal if any differences observed in clinical outcomes across PFNA, DHS and GN, it may be prudent to place extra emphasis on other factors in the decision-making process, namely cost, fracture types, and familiarity with the design and instruments. The device costs vary widely among countries and individual healthcare facilities; however, it is almost certain that the prices of intramedullary nailing including PFNA and GN are relatively higher than DHS [34]. The economic decision of the treatment options are important consideration for individual patients, care provider and hospital. The types of fracture are another important factor in the selection of the treatment options. According to the AO fracture classification system, type A1 is universally considered stable and type A3 (reverse obliquity fractures) is generally considered unstable. A2 fractures are less clear, but a generally accepted opinion is that A2-1 fractures are stable whereas A2-2 and A2-3 fractures are unstable. For stable fractures, either of extramedullary and intramedullary fixations could provide a safe and effective alternative [35]. However, for the unstable fractures, several biomechanical and clinical studies [36-38] demonstrated that intramedullary implant is superior with less fracture related complications and implant failures. In one recent study

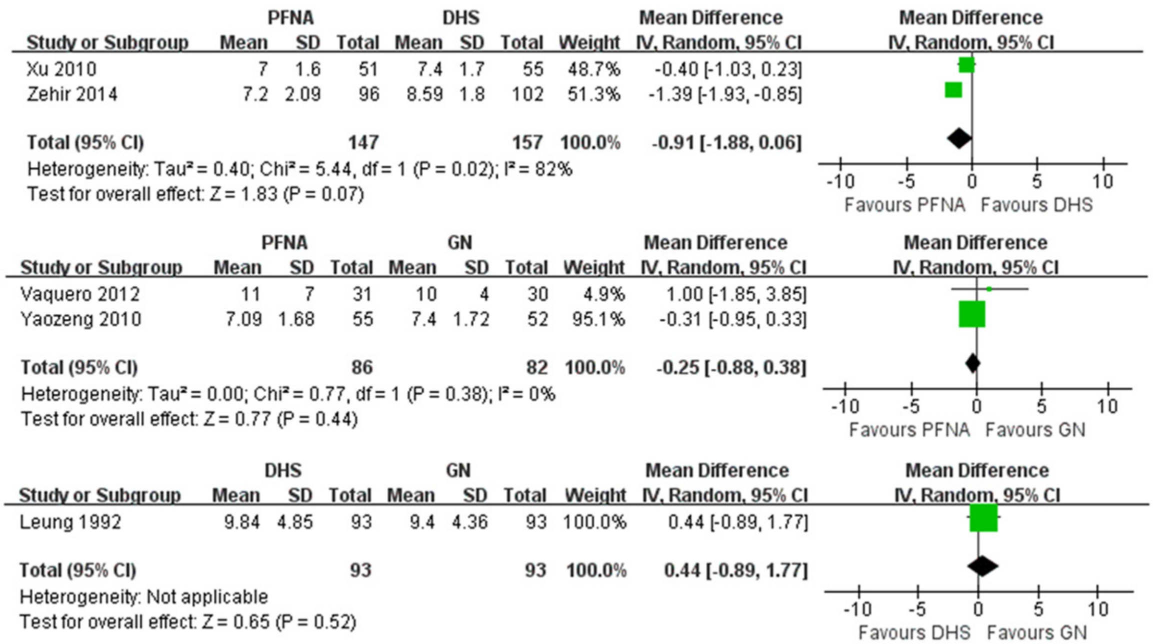


Figure 11. The forest plots of pair-wised meta-analysis comparing length of hospital stay across the three implants. IV = inverse variance, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

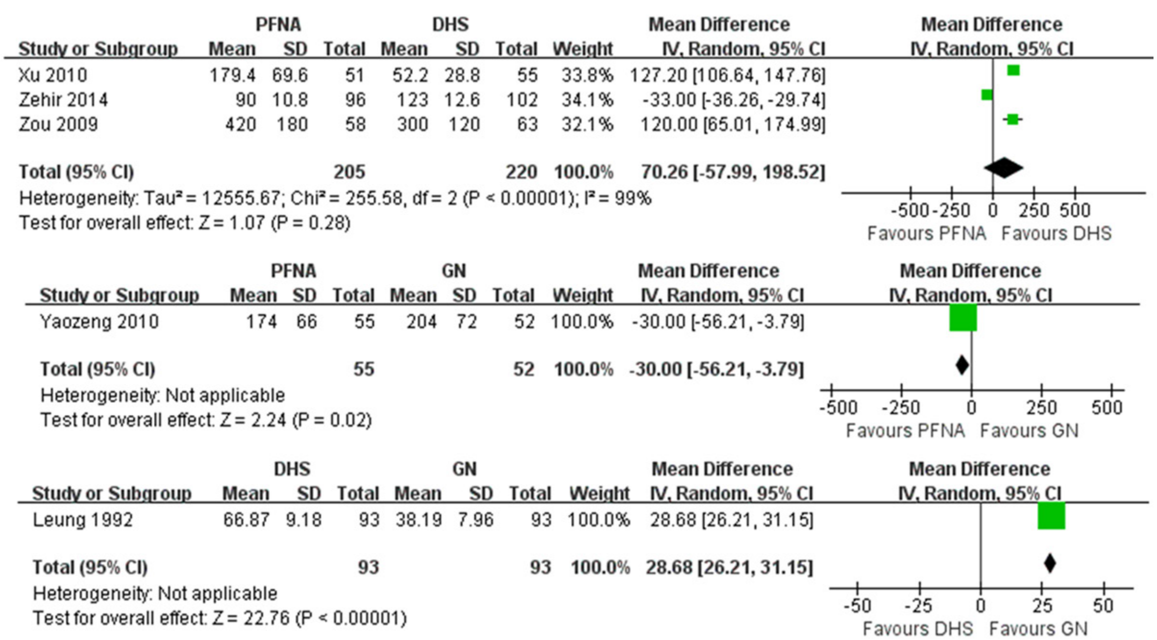


Figure 12. The forest plots of direct comparison evidence for fluoroscopy time across the three implants. IV = inverse variance, PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

[34], Swart et al. conducted a cost-effectiveness analysis of fixation options for intertrochanteric fractures and concluded that sliding hip screw is more cost-effective for stable fractures, whereas intramedullary nail fixation is more cost-effective for reverse obliquity fractures.

In conclusion, our systematic review and network meta-analysis does not support the supe-

Table 9. Mean differences of fluoroscopy time for direct-comparison meta-analysis and network meta-analysis

PFNA	-50.14 (-151.66-49.70)	-25.22 (-167.14-117.29)
70.26 (-57.99-198.52)	DHS	25.12 (-116.38-167.81)
-30.00 (-56.21- -3.79)	28.68 (26.21-31.15)	GN

For fluoroscopy time, mean differences (MDs) lower than 0 favor the column-defining treatment. Direct comparisons were shown in the lower left. Indirect comparisons were shown in the upper right. Abbreviation: PFNA = proximal femoral nails antirotation, DHS = dynamic hip screws, GN = Gamma nails.

riority of PFNA to other fixation strategies for intertrochanteric fractures. In light of this information, surgeons should consider about other factors such as cost, fracture types, familiarity with the design and instruments to make the appropriate choice for the treatment of intertrochanteric fractures. Future studies with high methodologic quality are required to confirm the conclusion and better inform clinical decision-making.

Disclosure of conflict of interest

None.

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