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REVIEW ARTICLE

Hybrid surgery for multilevel cervical degenerative disc diseases: a systematic review of biomechanical and clinical evidence

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Abstract
Purpose The optimal surgical technique for multilevel cervical degenerative disc diseases (DDD) remains controversial. Hybrid surgery (HS) incorporating anterior cervical discectomy and fusion (ACDF) and cervical disc replacement (CDR) is increasingly performed for cervical DDD. This study aims to evaluate the biomechanical and clinical evidence available for HS and to provide a systematic review of current understanding of HS.
Methods This systematic review was undertaken by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. Multiple databases and online registers of clinical trials were searched up to February 2014. The biomechanical and clinical studies on HS for cervical DDD written in English were included. Two authors independently assessed methodological quality and extracted data.
Results Fifteen studies including eight biomechanical studies and seven clinical studies were indentified. The biomechanical studies showed that HS was benefit to motion preservation of the operative levels and revealed less adverse effect on adjacent segments. All clinical studies demonstrated improvement in validated functional scores after HS. Segment motion and immobilization were achieved at the arthroplasty level and arthrodesis level, respectively. Postoperative assessments and complication rate were similar or in favor of HS when comparing with ACDF or CDR. However, the overall quality of evidence for HS was low to very low.
Conclusions There is a paucity of high quality evidence for HS. HS may be a safe and efficacious technique to benefit a select group of multilevel cervical DDD, which is needed to be confirmed by further prospective, randomized controlled trials.

Keywords Anterior cervical discectomy and fusion · Cervical disc replacement · Hybrid surgery · Degenerative disc diseases · Systematic review

Introduction

Anterior cervical discectomy and fusion (ACDF), a gold standard procedure, has been widely performed for cervical degenerative disc diseases (DDD) unresponsive to conservative treatment. ACDF can provide excellent fusion rate and clinical benefits [1, 2]. However, ACDF alters the normal biomechanics of the cervical spine, decreases mobility at the fused segments and increases motion at the adjacent levels especially in multilevel DDD, which may result in the acceleration of adjacent segment degeneration (ASD) and the need for further surgery in the long term [3–6]. Cervical disc replacement (CDR), an alternative technique for ACDF, is designed to preserve the motion of the treated level and to prevent

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overload of the adjacent discs and subsequent ASD [7, 8]. However, there is no strong evidence to support that CDR benefits over ACDF for cervical DDD especially lacking of long-term follow-up [1, 2, 9, 10]. Therefore, the optimal surgical technique for cervical DDD remains controversial.

Considering multilevel DDD, ACDF involving more fused levels leads to greater loss of mobility in operative levels, so benefits for adjacent segments may be more important than single-level DDD [11, 12]. Although CDR could be an attractive procedure to treat multilevel DDD, strict indications, hypermobility of the operative levels and higher medical cost may limit the application of multilevel CDR [8, 13, 14]. Recently, hybrid surgery (HS), a combination of fusion and non-fusion technique, has been introduced to clinical practice and increasingly applied for multilevel cervical DDD [13, 15]. This technique is based on the fact that ACDF or CDR may not be appropriate to every level because the degree of degeneration at each level is not always the same in multilevel DDD [8, 14]. HS aims to tailor ACDF or CDR to the selected levels for preserving segmental motion of the cervical spine, avoiding long-level fusion and preventing further ASD [13, 15, 16].

HS is an emerging procedure with need to evaluation. However, appropriate evidence for this increasing use is currently lacking. The objective of this systematic review is to identify the biomechanical and clinical studies on HS, summarize the current concepts and provide a foundation of evidence on the safety and efficacy of HS in the treatment of multilevel cervical DDD.

Materials and methods

This study was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [17].

Information sources

The literature search was performed to identify all available published articles (from January 1960 to February 2014) by searching electronic databases, including Pubmed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews. The unpublished trials were also searched for using clinical trials repositories, including the National Institute of Health, the National Research Register and Current Controlled Trials. The reference lists of the included studies were reviewed for further studies that met the eligibility criteria.

Search strategy

The search firstly used Mesh terms, including "arthroplasty", "arthrodesis" and "cervical vertebrae", and then a secondary free search was performed using multiple keywords, comprising "cervical disc", "cervical spine", "hybrid", "arthroplasty", "prosthesis", "replacement", "arthrodesis", "fusion", "cage" and "plate", to ensure inclusion all possible studies. The search was conducted by two dependent reviewers, with the limitation of English language. The abstract of any study potentially relevant to the topic was reviewed. The full texts were obtained if inadequate information was acquired from the abstracts. Disagreements were resolved by discussion, and a third reviewer was consulted for the final decision when necessary.

Inclusion and exclusion criteria

The eligible studies should meet the following inclusion criteria: (1) adult patients with degenerative disc diseases of the cervical spine; (2) clinical studies with single-stage HS combining ACDF and CDR, and biomechanical studies incorporating fusion and non-fusion technique; (3) published or unpublished studies written in English. This review excluded studies focused on patients with prior cervical surgery, skeletally immature individuals, pathological or inflammatory diseases. For studies with duplicate information, the prior papers with less data were excluded. Articles with five or less interested patients were excluded. Reviews and expert opinions were excluded if no original patient series was available.

Data extraction

For the included studies, two reviewers carefully read the full text of each study and independently extracted data. All extracted information was imported into a standardized spreadsheet. Disagreements between reviewers were resolved by discussion. A third reviewer was consulted if necessary. Information extracted included year of publication, country, study type, population demographics, trial duration, indications/contraindications, selection criteria of ACDF or CDR in HS, surgical information, perioperative outcomes, biomechanical and functional outcomes, and complications.

Risk of bias assessment

Following the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0), RCT was evaluated using Cochrane collaboration's tool for assessing the risk of bias, and non-RCTs was assessed by Methodological Index for

Non-Randomized Studies (MINORS) form [18, 19]. The bias assessment tool of Cochrane collaboration involved six key domains: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. The risk of bias was categorized as low risk, high risk or unclear risk. Bias assessment was carried out using RevMan 5.2.10 software (Cochrane Collaboration, UK). The MINORS was a validated instrument for assessing the quality of comparative and non-comparative non-RCT studies in surgery. The total score is 16 points for non-comparative studies and 24 points for comparative studies. Two reviewers independently assessed the methodological quality of each included clinical study. Disagreement was resolved by means of discussion, with arbitration by a third reviewer, when differences of opinion remained.

Quality assessment

The quality of evidence was assessed according to the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group [20–22]. The evidence grades are divided into the following categories: (1) high, which indicates that further research is very unlikely to change confidence in the effect estimate; (2) moderate, which indicates that further research is likely to significantly alter confidence in the effect estimate and may change the estimate; (3) low, which indicates that further research is very likely to significantly change confidence in the effect estimate and to change the estimate; and (4) very low, which indicates that any effect estimate is uncertain.

Data synthesis

A meta-analysis and comparison were conducted if two or more included studies involved clinical and statistical homogeneous results. When not possible, due to small amount of studies or heterogeneity, a qualitative descriptive analysis was performed.

Results

Literature search

The flow diagram of study selection is shown in Fig. 1. A total of 15 studies met our inclusion criteria, including 8 biomechanical studies [23–30] and 7 clinical studies [13, 15, 16, 31–34]. In the biomechanical studies, there were six cadaveric studies, one finite element analysis (FEA) and one combined study of cadaver and FEA. In the clinical studies, one RCT, three comparative studies and three non-comparative studies were identified. Other detailed information from each study is list in Tables 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

Biomechanical studies

General information of the biomechanical studies

In the biomechanical studies [23–30] (Table 1), arthroplasty was achieved by ProDisc-C, Discover or PCM in HS, while fusion was performed by anterior plate, screw–rod system or external fixator. There are six studies for 2-level HS and two studies for 3-level HS. The main concern on the hybrid constructs was the spinal kinematics, including the total range of motion (ROM) of the entire test cervical segment, the ROM at the operative and adjacent levels. Another concern was the effect of HS on the surrounding tissues, including the adjacent IDP and the stress in the endplate. The stiffness of hybrid construct, spinal buckling and facet load were also studied. A summary of these studies is shown in Tables 1 and 2.

Total ROM of the entire cervical segment

Compared with intact construct, no statistically significant difference in term of global ROM was observed in the hybrid construct [23–25, 27]. The finite element study revealed that the entire segment ROM in flexion extension (FE) decreased by 18.9 % in HS but was much closer to intact construct than the 2-level fusion construct in which the ROM decreased by 39.7 % [30].

ROM at the index levels

The ROM in HS significantly increased at the arthroplasty level and decreased at the arthrodesis level compared with the intact construct [25, 26, 30]. Therefore, the combined ROM of arthroplasty and arthrodesis levels was similar to that of the intact spine [24, 27]. However, inconformity was reported. Barrey et al. [23] revealed that HS not only caused significant reduction of ROM at the arthrodesis level in FE, axial rotation (AR) and lateral bending (LB) but also in AR and LB at the arthroplasty level, and Martin et al. [28] reported that the decrease in motion of the arthroplasty level was statistically significant for hybrid construct with C3–C4 arthroplasty and C4–C6 arthrodesis.

The location of the arthroplasty, whether above or below the arthrodesis, did not significantly affect the motion response of the arthroplasty in the 2-level hybrid constructs [27]. However, the study for 3-level hybrid constructs showed that the location and number of arthroplasty would affect the buckling. Arthroplasty at the caudal-most level resulted in significantly greater buckling than arthroplasty

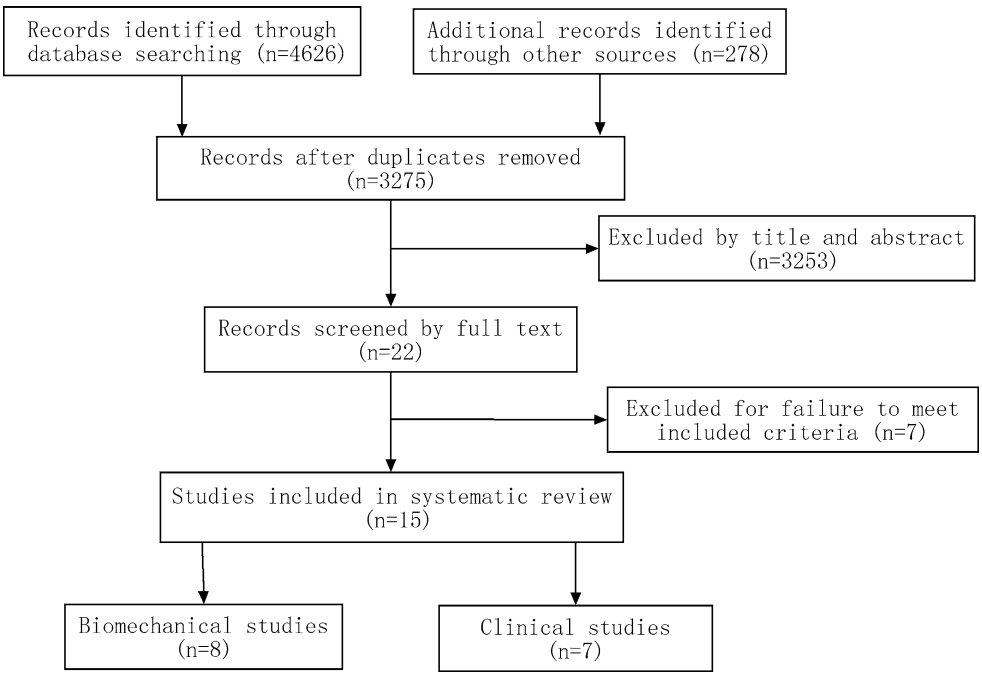

Fig. 1 The flow chart of study selection

Table 1 Characteristics of biomechanical studies

References	Study type	Index levels	Devices	Test protocol	Parameters
Zhao et al. [30]	FEA	2-level: C4–5, C5–6: FA	ProDisc-C, allograft/plate	74 N + 1.8 Nm	ROM, adjacent IDP
Safavi-Abbasi et al. [29]	Cadaveric	3-level: C4–5, C5–6, C6–7: FAA, AFA, AAF, FFA, FAF, AFF	ProDisc-C, screw–rod system	Displacement control protocol combined with 74 N compression	Buckling
Barrey et al. [23]	Cadaveric	2-level: C4–5, C5–6: AF	Discover, cage/plate	Pure 2.0 Nm and displacement control protocol	ROM, adjacent IDP
Faizan et al. [26]	Cadaveric, FEA	2-level: C4–5, C5–6: FA	Discover, plate	73.6 N + varying moment	ROM, facet loads, endplate stresses
Lee et al. [27]	Cadaveric	2-level: C4–5, C5–6: FA C5–6, C6–7: AF	PCM, external fixator	75 N + 1.5 Nm and displacement control protocol	ROM
Martin et al. [28]	Cadaveric	3-level: C3–4, C4–5, C5–6: AFF	ProDisc-C, external fixator	150 N + 1.5 Nm and displacement control protocol	ROM, Peak FE moment
Cho et al. [24]	Cadaveric	2-level: C5–6, C6–7: AF, FA	ProDisc-C, cage/plate	100 N + 2.0 Nm	ROM
Cunningham et al. [25]	Cadaveric	2-level: C5–6, C6–7: AF	PCM, cage/plate	Panjabi hybrid testing protocol	ROM

F fusion, *A* arthroplasty, *FEA* finite element analysis, *IDP* intradiscal pressure, *ROM* range of motion, *FE* flexion–extension

at cranial-most or middle level, and buckling was least for single-level arthroplasty while greatest for 3-level arthroplasty [29].

ROM at the adjacent levels

There remains controversy in terms of the ROM at adjacent levels. Cunningham et al. [25] and Lee et al. [27] reported that no statistical difference in adjacent-level motion was observed from HS and intact groups, and Zhao et al. [30] revealed that the reduction of ROM at adjacent level was <10 %. Barrey et al. [23] revealed that statistically significant change was observed in AR while no statistically significant change was observed in FE and LB, but Cho et al. [24] reported that hybrid constructs showed statistically significant alteration in LB at superior adjacent level. However, Faizan et al. [26] showed that the ROM increased by up to 30 and 40 % at the superior and inferior

adjacent levels, respectively, and an increase in motion was observed at the adjacent C2–C3 segment in the 3-level hybrid construct [28]. When considering the contribution of adjacent levels to global ROM, statistically significant changes were noted at lower level for HS [23]. The primary inconformity was due to the different test control protocols among the studies. Displacement control protocol always exhibited a higher ROM at adjacent levels in the hybrid or 2-level fusion constructs comparing with load control protocol [26, 30].

Adjacent IDP and endplate stress

The increase of IDP at superior adjacent level for HS was lower than that for 2-level fusion (a factor of 2.3 versus 6.7) [23]. Similarly, Zhao et al. [30] compared HS with 2-level fusion and revealed that the maximal IDP increased by more than 40 % at adjacent levels in the fusion model, whereas it is increased by <10 % in the hybrid construct. Moreover, Faizan et al. [26] found that adjacent level motions, facet loads and endplate stress in HS were closer to that in the intact construct rather than the 2-level fusion model.

Stiffness of the cervical spinal segment

Faizan et al. [26] revealed that the stiffness of HS was close to intact construct during spinal bending motions except in extension. Lee et al. [27] reported that the spine with a hybrid construct required significantly less extension moment than the spine with a 2-level fusion to reach the same extension end point. Flexion and extension moments needed to bring the cervical spine to similar C2 motion endpoints significantly increased for the hybrid construct with an arthroplasty above a 2-level fusion compared to arthroplasty alone, and lordotic fusion required significantly greater flexion moment, whereas straight fusion required significantly greater extension moment [28].

Clinical studies

General information of the clinical studies

In total, seven clinical studies with 217 patients (139 male and 78 female) were included in this review [13, 15, 16, 31–34]. These studies were from America, China, Italy, Korea, and Singapore. The mean age of included patients ranged from 45.7 to 55.3 years. The duration of follow-up was from 8 to 84 months. A total of 171 patients received HS, including 125 two-level, 44 three-level and 2 four-level surgery. The artificial discs including ProDisc-C, Bryan, Prestige ST, Mobi-C and Prestige LP were used to perform CDR of HS, while cage with or without plate and Zero-P were for ACDF of HS. The detailed information from each study is summarized in Table 3.

Risk of bias

Among the included studies, there was only one RCT [32] and six non-RCTs including three comparative studies and three non-comparative studies [13, 15, 16, 31, 33, 34]. The risk of bias of the included studies is illustrated in Fig. 2 and Table 4. For the RCT, randomization was conducted using the odd or even hospital number [32]. It was denoted as high risk of selection bias, including random sequence generation and allocation concealment [19]. Regarding to the non-RCTs, the mean MINORS score was 14.7 (range from 13 to 16) for the comparative studies [13, 16, 33] and 9.3 (range from 9 to 10) for non-comparative studies [15, 31, 34], which were accounted for 61 % (14.7/24) and 58 % (9.3/16) of the scores, respectively. These results indicated that the non-RCTs also had a high risk of bias resulting from study design limitations.

Quality of evidence

The quality of evidence is shown in Table 5. Only RCT was downgraded by two levels following the GRADE guidelines [19–22], due to very serious limitations in study design and implementation [19, 32]. The RCT was graded as low quality. The quality of the observational studies [13, 15, 16, 31, 33, 34] was not upgraded and denoted as very low due to the less rigorous methodology [21]. Overall, there was only low to very low quality evidence for HS.

Indications and contraindications

All included studies reported indications/contraindications of HS [13, 15, 16, 31–34]. The main indication in most of the studies was symptomatic multilevel cervical DDD with radiculopathy or myelopathy (Table 6). There were three studies indicating that these patients should be failed to conservative treatment [13, 32, 33], two of which suggested that the duration of conservative treatment should be over 6 weeks [32, 33]. There were no consensus contraindications among the included studies, including previous surgery in cervical spine, obvious instability, osteoporosis, deformity, inflammatory diseases, posterior cervical stenosis, spondylotic change, obvious degeneration at non-operated levels and the same exclusion criteria of CDR or ACDF [13, 15, 16, 31–34].

For the selection criteria of CDR or ACDF in HS, the included studies demonstrated that there are at least one mobile and non-spondylotic level for CDR and others for ACDF [13, 15, 16, 31–34] (Table 6). If multiple levels met the criteria of CDR, the level with greater physiologic

Table 2 Summary of biomechanical results

References	Total ROM	ROM at the index levels	ROM at the adjacent segments	Other results
Zhao et al. [30]	Decreased by 18.9 % for HS while 39.7 % for TLF	Increased by more than 50 % at the arthroplasty level, but decreased by more than 90 % at the arthrodesis level	Decreased by 8.1 % in SAS and 2.1 % and IAS for HS, and increased by 0.1 and 8.3 % for TLF	Adjacent IDP increased by 5 % in IAS and 10 % in IAS for HS, and 44 and 41 % for TLF
Safavi-Abbasi et al. [29]	NA	NA	NA	Greatest neutral buckling in 3-level arthroplasty followed by 2- and 1-level arthroplasty. Greater buckling in FFA construct comparing with AFF or FAF in 3-level arthroplasty
Barrey et al. [23]	No significance between HS and the intact	Significant reduction in FE, AR, LB at the arthrodesis level and in AR and LB at the arthroplasty level	No significance as compared to the intact except in AR. Significant changes in contribution to global ROM was observed at lower level in HS comparing with the intact	Adjacent IDP for HS increased from 2.3 to 5.3 bar in SAS, but increased from 1.3 to 8.6 bar for TLF
Faizan et al. [26]	NA	ROM at the arthroplasty level in HS increased by up to 40 % as compared to the intact to compensate for the lost motion due to arthrodesis	Increased by up to 30 and 40 % at the SAS and IAS, respectively	The stiffness of HS was close to the intact during bending motions except in extension
Lee et al. [27]	HS using the PCM maintains the total ROM in FE comparing with the intact	The location of the fusion (above or below the arthroplasty) did not significantly affect the motion response of the arthroplasty in HS	TLF significantly increase of the motion demands on the non-operated segments as compared to HS	The spine with a HS required significantly less extension moment than the spine with a TLF to reach the same extension end point
Martin et al. [28]	NA	The decrease in motion of arthroplasty level was significant for both lordotic and straight fusions and the fusion allowed reduction of segmental motion across arthrodesis levels	Compensatory increase in motion was observed at the SAS	Flexion and extension moments needed to achieve similar motion endpoints significantly increased for the HS as compared to arthroplasty alone
Cho et al. [24]	No significance comparing with the intact	The combined ROM for HS is similar to the intact spine in EF and LB	No significance at the SAS comparing with the intact except in LB	NA
Cunningham et al. [25]	No significant change comparing with intact construct	Significant increase at the arthroplasty level for HS and decrease at the fusion level comparing with the intact and arthroplasty alone	No significance between HS and the intact	NA

HS hybrid surgery, *SAS* superior adjacent segment, *IAS* inferior adjacent segment, *TLF* two-level fusion, *ROM* range of motion, *F* fusion, *A* arthroplasty, *FE* flexion extension, *AR* axial rotation, *LB* lateral bending, *IDP* intradiscal pressure

motion received CDR (C5–C6 > C4–C5 > C6–C7 > C3–C4) [13, 31, 33]. Moreover, to make precise selection criteria for CDR or ACDF at each level, a decision-making algorithm was developed by Barbagallo et al. [15]. However, the final decision on CDR or ACDF at each level was determined by the intra-operative findings [15].

Perioperative characteristics

Operation time and blood loss were evaluated in four studies [13, 16, 32, 34] (Table 7). Ren et al. [34] reported case series of 22 two-level and 4 three-level HS and demonstrated that the average operation time was 130 min and blood loss was 130 ml. In 3-level DDD, Kang et al. [32] revealed that HS was associated with less operative time and less blood loss when comparing with ACDF, but there was no significance between groups. In 2-level DDD, Shin et al. [13] found that HS required significantly less operative time and less blood loss than ACDF. However, Hey et al. [16] conducted a three-arm study (ACDF, HS and CDR) in patients with 2- and 3-level cervical DDD and revealed that the duration of operation was shortest in ACDF group, followed by HS and CDR, and significances were revealed when comparing ACDF with HS or CDR,

Table 3 Characteristics of clinical studies

References	Country	Study design	Sample size	Mean age (years)	Gender (M/F)	No. of HS	Devices of HS	Follow-up (m)
Hey et al. [16]	Singapore	PCS	HS/ACDF/CDR: 7/7/7	HS/ACDF/CDR: 51/48/46	HS: 3/4 ACDF: 4/3 CDR: 5/2	2-level: 4 3-level: 3	ProDisc-C, cage	24–45
Kang et al. [32]	China	RCT	HS/ACDF: 12/12	HS/ACDF: 53.6/55.3	HS: 8/4 ACDF: 7/5	3-level: 12	ProDisc-C, cage/Zero-P	24–48
Lee et al. [33]	Korea	RCS	HS: 51	HS: 48.2	40/11	2-level: 41 3-level: 10	ProDisc-C/Bryan, plate	24–84
Ren et al. [34]	China	NCS	HS: 26	HS: 47	17/9	2-level: 23 3-level: 3	Bryan, cage	24–47
Cardoso et al. [31]	America	NCS	HS: 31	HS: 50	18/13	2-level: 22 3-level: 9	Prestige ST, cage/plate	8–29
Barbagallo et al. [15]	Italy	NCS	HS: 24	HS: 46.7	15/9	2-level: 15 3-level: 7 4-level: 2	ProDisc-C/Prestige LP/Bryan, cage	12–40
Shin et al. [13]	Korea	PCS	HS/ACDF: 20/20	HS/ACDF: 48/45.7	HS: 10/10 ACDF: 12/8	2-level: 20	Mobi-C, cage	>24

RCT randomized controlled trial, *PCS* prospective comparative study, *RCS* retrospective comparative study, *NCS* non-comparative study, *HS* hybrid surgery, *ACDF* anterior cervical discectomy and fusion, *CDR* cervical disc replacement

Table 4 The MINORS scores for non-RCTs

Items[a]	Comparative studies			Non-comparative studies		
	Hey et al. [16]	Lee et al. [33]	Shin et al. [13]	Ren et al. [34]	Cardoso et al. [31]	Barbagallo et al. [15]
1. A clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	1	1	1	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	1	1	1	1	1	1
5. Unbiased assessment of the study endpoint	0	1	1	1	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	1	1
7. Loss to follow-up <5 %	2	1	2	1	1	1
8. Prospective calculation of the study size	0	0	0	0	0	0
Additional criteria for comparative studies						
9. An adequate control group	2	1	1	NA	NA	NA
10. Contemporary groups	1	1	1	NA	NA	NA
11. Baseline equivalence of groups	2	0	2	NA	NA	NA
12. Adequate statistical analyses	2	1	1	NA	NA	NA
Total scores[b]	16	13	15	10	9	9

MINORS Methodological Index for Non-Randomized Studies, *RCT* randomized controlled trials, *NA* not available

[a] The items are scored as follows: 0 (not reported); 1 (reported but inadequate); or 2 (reported and adequate)

[b] Maximum MINORS score is 24 for comparative studies and 16 for non-comparative studies

Table 5 Grading of clinical studies following GRADE guidelines

References	Study design	Risk of bias	Indirectness	Imprecision	Publication bias	Large effect	Plausible residual confounding	Total	Quality of evidence
Hey et al. [16]	Observational study	−1	0	N/A	−1	0	0	−2	Very low
Kang et al. [32]	Randomized controlled trial	−2	0	N/A	0	0	0	−2	Low
Lee et al. [33]	Observational study	−1	0	N/A	−1	0	0	−2	Very low
Ren et al. [34]	Observational study	−2	0	N/A	−1	0	0	−3	Very low
Cardoso et al. [31]	Observational study	−2	0	N/A	−1	0	0	−3	Very low
Barbagallo et al. [15]	Observational study	−2	0	N/A	−1	0	0	−3	Very low
Shin et al. [13]	Observational study	−1	0	N/A	−1	0	0	−2	Very low

Table 6 Indications and contraindications for HS

References	Indications	Contraindications
Hey et al. [16]	Multilevel prolapsed cervical discs. Some levels requiring replacement and others fusion	Obvious degeneration at non-operated levels
Kang et al. [32]	Three-level consecutive cervical DDD over 6 weeks failed conservative treatment	Obvious instability, osteoporosis and inflammatory diseases
Lee et al. [33]	Multilevel consecutive cervical DDD over 6 weeks failed conservative treatment. CDR at a mobile and non-spondylotic segment determined by dynamic X-rays and CT scans. CDR performed in greater physiologic motion segment when multiple levels meeting CDR	Exclusion criteria of CDR or ACDF, previous surgery with device, axial neck pain, significant deformity, instability, ossification of posterior longitudinal ligament and active infection
Ren et al. [34]	Multilevel cervical disc herniation with symptomatic myelopathy or radiculopathy	NA
Cardoso et al. [31]	Radiculopathy or myelopathy. CDR performed in greater physiologic motion segment when multiple levels meeting CDR	Previous cervical fusion and exclusion criteria of CDR
Barbagallo et al. [15]	Multilevel symptomatic DDD with radiculopathy or myelopathy. CDR or ACDF at treated level according to a decision-making algorithm and intra-operative findings	Spondylotic changes and exclusion criteria of CDR
Shin et al. [13]	Two-level consecutive DDD with radiculopathy or myelopathy failed conservative treatment. At least a mobile and non-spondylotic level for CDR. CDR performed in greater physiologic motion segment when multiple levels meeting CDR	Facet syndrome, posterior cervical stenosis, deformity, osteoporosis, infection and spondylotic changes without mobility in both levels

HS hybrid surgery, *ACDF* anterior cervical discectomy and fusion, *CDR* cervical disc replacement, *DDD* degenerative disc diseases, *NA* not available

and hemoglobin drop postoperatively representing perioperative blood loss was least in CDR group, followed by HS and ACDF, and statistically significant difference was only observed between ACDF and CDR.

Postoperative managements

Four of the included studies described postoperative managements [15, 16, 32, 34] (Table 8). Regarding to rehabilitation, wearing a soft collar for approximate 1 month postoperatively was noted in three studies [15, 16, 34], and Ren et al. [34] also suggested intermittently flexion and extension exercise during the period. Kang et al. [32] developed a standardized rehabilitation program while without describing detailed information. Moreover, postoperative medicine was indicated in two studies [15, 34]. Celecoxib 200 mg twice daily for 10 days was postoperatively conducted by Ren et al. [34]. Barbagallo et al. [15] reported that anti-inflammatory drugs were not routinely used for 6 weeks postoperatively and oral analgesics were only administered when required.

Table 7 Perioperative outcomes

References	Operation time (min)	Blood loss (ml)
Hey et al. [16]	Mean 135, 195 and 197 for ACDF, HS and CDR, respectively, and significance between ACDF and HS or CDR	Mean 0, 0.7 and 1.2 g/l of hemoglobin drop for CDR, HS and ACDF, respectively, and significance between CDR and ACDF
Kang et al. [32]	Mean 118 and 126 for HS and ACDF, respectively, but no significance	Mean 324 and 357 for HS and ACDF, respectively, but no significance
Lee et al. [33]	NA	NA
Ren et al. [34]	130 (90–160)	130 (50–400)
Cardoso et al. [31]	NA	NA
Barbagallo et al. [15]	NA	NA
Shin et al. [13]	Mean 105, 127 min for HS and ACDF, respectively, and significance between groups	Mean 134 and 180 for HS and ACDF, respectively, and significance between groups

HS hybrid surgery, *ACDF* anterior cervical discectomy and fusion, *CDR* cervical disc replacement, *NA* not available

Table 8 Postoperative managements

References	Medicine	Rehabilitation
Hey et al. [16]	NA	Wearing a soft collar for 1 month
Kang et al. [32]	NA	A standardized rehabilitation program
Lee et al. [33]	NA	NA
Ren et al. [34]	Celecoxib 200 mg twice daily for 10 days	Wearing a cervical collar and intermittently flexion and extension exercise for 3–4 weeks
Cardoso et al. [31]	NA	NA
Barbagallo et al. [15]	Not routine anti-inflammatory drugs for 6 weeks and oral analgesics when required	Wearing a soft collar for 1 month
Shin et al. [13]	NA	NA

NA not available

Radiological outcomes

The ROM of the cervical spine was reported in five studies and shown significantly limited after surgery and then gradually recovered [13, 16, 31–33] (Table 9). In the comparative studies, no significances were revealed in cervical ROM when comparing HS to the control groups in two studies [16, 33]. However, significantly rapid recovery of ROM was shown in HS group compared to ACDF in the other studies [13, 32]. The adjacent level motion was evaluated in three studies [13, 32, 33]. Kang et al. [32] found that the superior and inferior adjacent ROM significantly decreased postoperatively and gradually increased in both HS and ACDF, and statistically significant increase was noted in ACDF group at 12 and 24 months postoperatively relative to preoperative motion. Moreover, ACDF group showed a statistically significant increase of the adjacent motion at 12 and 24 months comparing with HS. Lee et al. [33] demonstrated that the inferior adjacent ROM of HS was significantly increased comparing to the superior. Shin et al. [13] reported that there was no significance between HS and ACDF according to the superior adjacent motion, however, ACDF had a statistically significant increase of the lower adjacent motion at 3, 6, 12 and 24 months postoperatively. Additionally, ROM of the arthroplasty level in HS was reported in three studies and shown good motion preservation [15, 33, 34].

Functional scores

All the functional scores were significantly improved postoperatively when comparing with the preoperative scores in the reported studies [13, 15, 16, 32–34] (Table 9). The comparative studies showed that there were no statistically significant differences according the functional scores compared to the control groups in 2- and 3-level DDD [16, 32, 33]. Only one study [13] demonstrated statistically significant recovery of neck disability index (NDI) at 12 and 24 months postoperatively and visual

Table 9 Postoperative outcomes

References	Radiological outcomes	Functional scores	Other outcomes
Hey et al. [16]	$ROM_{C3–C7}$, $ROM_{arthroplasty}$: no significance across the groups	NDI, VAS, EQ-5D: no significance across the groups	Hospitalization: 3, 5 and 7 days for CDR, HS and ACDF, respectively, and significance across the groups
			Days off work: 54, 73 and 107 days for HS, CDR and ACDF, respectively, but only significance between HS and ACDF
Kang et al. [32]	$ROM_{C2–C7}$: significantly decreased at 1, 3 and 6 m and restored largely at 24 m for HS, significantly decreased at 1, 3, 6, 12 and 24 m for ACDF, and significantly increased when comparing HS to ACDF	NDI, VAS: significantly improved for both HS and ACDF, but no significance between HS and ACDF	NA
	$ROM_{adjacent\ segment}$: significantly decreased at 1 m and no significance at 3, 6, 12 and 24 m for HS, significantly decreased at 1 m, increased at 3 and 6 m and significantly increased at 12 and 24 m for ACDF, and increased at 12 and 24 m comparing ACDF with HS		
Lee et al. [33]	$ROM_{C2–C7}$: significantly limited postoperatively and then gradually recovered, but no significance between 2- and 3-level HS	NDI, VAS: significant improvement for both 2- and 3-level HS, but no significance between groups	NA
	$ROM_{adjacent\ segment}$: the lower significant increased comparing with the upper		
	$ROM_{arthroplasty}$: no significance between 2- and 3-level HS		
Ren et al. [34]	$ROM_{arthroplasty}$: 9.5°	JOA, NDI: significant improvement	Hospitalization: 10 days (9–13 days)
		Odom's criteria: 84.6 %.	
Cardoso et al. [31]	Cervical lordosis: no significant change	NA	NA
	$ROM_{C2–C7}$: significantly decreased for 2-level HS, but no significance for 3-level HS		
Barbagallo et al. [15]	$ROM_{arthroplasty}$: 3°–15°	NDI, SF-36: significant improvement	NA
		Nurick: improvement in all but three patients	
Shin et al. [13]	$ROM_{C2–C7}$: significantly decreased at 1 m and gradually recovered in both HS and ACDF, and significant rapid recovery comparing HS with ACDF	NDI: improvement in both groups, and significant recovery comparing HS with ACDF at 12 and 24 m	NA
	$ROM_{adjacent\ segment}$: no significance in the upper between HS and ACDF, but significant increased in the lower at 3, 6, 12 and 24 m comparing ACDF with HS	VAS: improvement in both groups, significant recovery for HS at 1 and 12 m in neck VAS, but no significance in arm VAS	

HS hybrid surgery, *ACDF* anterior cervical discectomy and fusion, *CDR* cervical disc replacement, *ROM* range of motion, *NDI* neck disability index, *VAS* visual analog scale, *JOA* Japanese orthopaedic association scale, *NA* not available

Table 10 Complications

References	HS	ACDF	CDR
Hey et al. [16]	1 residual limb symptoms 1 dysphagia	1 residual limb symptoms	1 residual limb symptoms
Kang et al. [32]	1 heterotopic ossification	1 further surgery due to ASD 2 asymptomatic implant subsidence	NA
Lee et al. [33]	0	NA	NA
Ren et al. [34]	2 heterotopic ossification	NA	NA
Cardoso et al. [31]	7 dysphasia 1 vocal cord paralysis	NA	NA
Barbagallo et al. [15]	2 heterotopic ossification	NA	NA
Shin et al. [13]	0	0	NA

HS hybrid surgery, *ACDF* anterior cervical discectomy and fusion, *CDR* cervical disc replacement, *ASD* adjacent segment degeneration, *NA* not available

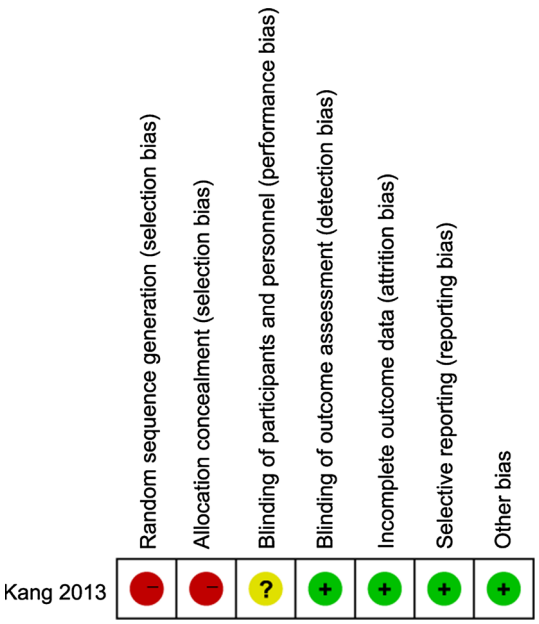

Fig. 2 Risk of bias in the RCT

analog scale (VAS) of the neck at 1- and 12-month follow-ups when comparing HS with ACDF in 2-level DDD.

Other outcomes

Length of hospitalization was evaluated in two studies [16, 34] (Table 9). Ren et al. [34] reported in-hospital stay was 10 days (range from 9 to 13). Hey et al. [16] found that the duration of hospitalization was shortest in CDR group, followed by HS and ACDF, and statistically significant difference was noted across the groups. Moreover, Hey et al. [16] also demonstrated that days off work were shortest in HS group, followed by CDR and ACDF, and significance was only found between HS and ACDF.

Complications

All include clinical studies evaluated the complications of HS. Among them, two studies reported no complication found in HS group [13, 33]. In all, there are 15 reported complications in HS group, including 8 dysphasias, 5 heterotopic ossifications, 1 vocal cord paralysis and 1 residual limb symptoms (Table 10).

Discussion

Cervical DDD has become one of the most controversial subjects in spine communities. To this day, most spine surgeons have always performed either a fusion or non-fusion technique, such as ACDF or CDR, to alleviate symptoms due to cervical DDD. However, different cervical levels always indicate different grades of degeneration [8, 14, 15]. Therefore, HS combining fusion and non-fusion technique may be a rational procedure for cervical DDD. To our knowledge, this is the first systematic review of biomechanical and clinical evidence on HS for multi-level cervical DDD. The main findings of the present study are (1) HS demonstrates biomechanical benefits in terms of motion preservation of the operative levels and less adverse affect on adjacent segments, and (2) HS may be a safe and efficacious alternative in appropriately selected patients with multilevel cervical DDD. However, it is need to be confirmed by further well-designed studies for only low to very low quality evidence available.

Current biomechanical evidence indicates that HS could maintain the combined motion of operative levels [24, 27], which shows no statistically significant difference from the

normal spine. Hence, HS demonstrates no obvious adverse affect on the cervical spinal kinematics, IDP in adjacent segments and facet joint force [23, 25, 27, 30]. In contrary to HS, 2-level fusion largely constrains ROM of operative levels and induced compensatory increase of motion at adjacent levels that may adversely increase the IDP [23, 30]. However, it cannot be proven that less decrease in motion resulted in less ASD, since a meta-analysis indicated no statistically significant difference in the rate of ASD was observed between CDR and ACDF based on available evidence [35]. Previous researches attributed ASD to the fusion-induced increasing IDP [36–38], despite that it is deemed to be associated with a progression of underlying disease of cervical degeneration [11, 39, 40]. However, there remains inconsistency on biomechanical performances of HS, since the biomechanical performances may be different with arthroplasty designs or testing conditions. Various testing methods have been used to investigate cervical spine mechanics [41]. In general, load control was applied in studies concerned the biomechanics of the operative segments [24, 26, 30], and displacement control was applied in studies concerned the biomechanics of the adjacent levels [23, 25, 27]. Based on the same testing protocols and normalization by comparing with intact construct, the biomechanical studies provided comparable results in some degree. Conservatively speaking, HS seems to be moderate to treat cervical DDD rather than bi-level fusion or bi-level arthroplasty according to biomechanical evidence.

Operative characteristics are important safety outcomes when considering the option of surgical techniques. Regarding the operation time and blood loss, HS shows inconsistent (similar, better or worse) results when comparing with ACDF [13, 16, 32]. One of the possible reasons for this is that operation time and blood loss are individualized outcomes, which may be associated with the treated levels, the procedures and the surgeons' skills [13, 16, 32, 34]. Therefore, there are no consistent results for these outcomes in this review, whereas all the authors of the included studies consider HS as a safe selection for multilevel cervical DDD.

Various measures, such as ROM, NDI, VAS and SF-36, have been developed to assess the efficacy of the surgical procedures in this review. Regarding with radiological outcomes, the ROM of cervical spine reaches an equivalent or better recovery in HS group comparing with ACDF or CDR group [13, 16, 32]. The ROM of adjacent segments in ACDF group is associated with a higher increase at the final follow-up in comparison with HS [13, 32, 33], especially in the lower adjacent segment [13, 33]. Arthroplasty level of HS shows a good motion preservation [15, 33, 34]. With regard to functional scores, postoperative improvement demonstrates that HS could reach a similar [13, 15, 16, 32–34] and even better outcomes in selected patients [32]. However, it should be noted that the clinical improvement may be mainly associated with decompression rather than the specific device [15, 33].

Complication rates differ among the included studies, ranging from 0 to 28.6 % [13, 15, 16, 31–34] while representing an overall complication rate of 8.8 % (15/171). Fortunately, HS shows no higher complication rates in the comparative studies [13, 16, 32], most of the complications are alleviated or recovered at the final follow-up and no further interventions are need [13, 15, 16, 31–34].

In comparison with ACDF, HS has theoretically advantages on less fusion levels and resultant adjacent segment pathology including degeneration and disease [42]. They represent radiographic characteristics and clinical manifestations, respectively. Biomechanical studies demonstrate that fusion induces hypermobility and increased stress at adjacent segments [4, 5, 43, 44], while arthroplasty maintains physiological motion and pressure at these segments [36, 37, 45]. However, there is no evidence to prove that fusion could increase adjacent segment pathology while arthroplasty decrease [35, 46]. Additionally, it also could not be concluded that adjacent segment degeneration is correlated to clinical disease, despite some patients develop symptomatic disease following fusion [47, 48]. Similarly in this study, HS shows beneficial effect on adjacent segments comparing with ACDF while no clinical evidence reveals the difference between groups. It may demonstrate that adjacent segment pathology is multifactorial, at least including biomechanics and a natural process [47, 48].

The interaction between arthroplasty and arthrodesis should be concerned. Biomechanical studies demonstrate that the kinematics of the arthroplasty adjacent to a single-level fusion is not significantly involved when compared to CDR alone [23, 27]. However, when the arthroplasty is adjacent to a 2-level fusion, it may be subjected to a more challenging biomechanical environment comparing with CDR alone [28, 49]. Since device failure or dislocation has not been found in the included studies yet, there was no clinical evidence to support the hypothesis of subsequent pseudoarthrosis adjacent to the arthroplasty or device failure adjacent to arthrodesis. However, it should be recognized that high quality studies with large sample size and long-term follow-up are necessary to confirm these conclusions.

There are several limitations to our review. First, although our best efforts in using multiple search strategy and available database to include all possible studies, publication bias which is common to all systematic reviews may be unavoidable. Second, the included studies have some important limitations. Most of the clinical studies are observational and the only one RCT is of methodological

weaknesses and small sample size. Various prostheses used in the included studies may induce related bias. Long-term follow-up results are not available and still need disclosing in the future. Third, due to lacking strong scientific evidence and obvious heterogeneity among the studies, a meta-analysis to statically strengthen the evidence could not be performed, and a descriptive systematic review was conducted instead.

Conclusion

This study provides an overview of the current knowledge on HS for multilevel cervical DDD. HS may be a safe and efficacious of HS to benefit certain patients with multilevel cervical DDD. However, there is insufficient evidence to draw a firm conclusion due to only low to very low quality evidence. As a new combination procedure, appropriate attention must be given to strict surgical indications, proper patient selection, improved surgical technique and associated complications. In this way, HS could have potential beneficial effects in select group of patients with cervical DDD. We believe that this systematic review will help spine surgeons to understand biomechanical and clinical characteristics of HS. However, further prospective, randomized controlled studies are needed to reach a more reliable conclusion.

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Conflict of interest None of the authors has any potential conflict of interest.

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