REVIEW PROTOCOL

1.Title

Efficacy and safety of hybrid surgery versus anterior cervical discectomy and fusion in multilevel cervical degenerative disc disease: A systematic review and meta-analysis

2.Background and Rationale

Cervical degenerative disc disease involving multiple levels can be managed surgically using various approaches. The traditional gold-standard technique, Anterior Cervical Discectomy and Fusion (ACDF), has been associated with potential complications such as adjacent segment disease (ASD) due to loss of motion at the fused levels.

Hybrid cervical spine surgery (HS) typically combines ACDF at some levels with cervical disc arthroplasty (CDA) at adjacent levels in order to preserve motion and potentially reduce the risk of ASD. Several comparative studies exist, but a comprehensive synthesis of outcomes is required.

Aim

This systematic review and meta-analysis will evaluate and compare the clinical efficacy, radiographic outcomes, and safety of hybrid surgery (HS) versus ACDF in patients with multi-level cervical degenerative disc disease.

3.Objectives

3.1. Primary Objectives

- To compare clinical outcomes (Neck Disability Index [NDI], Visual Analog Scale [VAS] for pain, arm, neck or combined, Japanese Orthopedic Association [JOA] score, Odom criteria) between hybrid surgery and ACDF in multi-level cervical degenerative disc disease.
- To compare radiological outcomes (cervical overall range of motion, superior and inferior adjacent segments range of motion)

3.2. Secondary Objectives

- To compare perioperative outcomes (operation time, blood loss)
- To compare complications (adjacent segment disease [ASD], heterotopic ossification [HO], Dural/cord injury, C5 palsy, implant subsidence, dysphagia/dysphonia, hematoma, infection).

4. Review question

In adult patients with multi-level cervical degenerative disc disease (**P**), how does hybrid surgery (**I**) compare to anterior cervical discectomy and fusion (ACDF) (**C**) in terms of efficacy and safety outcomes (**O**)?	
Population	Adult patients with multi-level cervical disc disease
Intervention	Hybrid surgery (HS)
Comparison	Anterior cervical discectomy and fusion (ACDF)
Outcome	Efficacy and safety outcomes: 1- Efficacy outcomes (primary outcome measures): Neck Disability Index [NDI], pain Visual Analog Scale [VAS], Japanese Orthopedic Association [JOA] score, Odom criteria, cervical overall range of motion, superior and inferior adjacent segments range of motion 2.Safety outcomes (secondary outcome measures): blood loss, operation time, and complications (adjacent segment disease [ASD], heterotopic ossification [HO], Dural/cord injury, C5 palsy, implant subsidence, dysphagia/dysphonia, hematoma, infection).

5. Methods

5.1. Protocol Registration

This protocol will be registered on an international prospective register of systematic reviews (**PROSPERO** at https://www.crd.york.ac.uk/prospero). Any significant amendments will be documented and explained in the final report.

5.2. Eligibility Criteria (PICO Framework)

PICO	Inclusion Criteria	Exclusion Criteria
Population	• patients diagnosed as multilevel (2 or 3) cervical degenerative disc disease indicated for anterior cervical discectomy • Adults (≥18 years) • No restriction on sex or ethnicity.	• Animal studies • In vitro human studies (including cadaver material). • studies including other pathologies than degenerative cervical disc disease like (neoplastic, infection, trauma) • Revision surgery • studies including single level or undetermined number of operated levels • studies reporting on special populations (e.g. Pregnant women).
Intervention	• **Hybrid surgery (HS)**: defined as combination of ACDF and cervical disc arthroplasty (CDA) at adjacent levels.	• Studies defining hybrid surgery other than combination of CDA+ACDF (e.g. corpectomy + ACDF)
Comparison	• Anterior Cervical Discectomy and Fusion (ACDF)	• studies not comparing HS to ACDF
Outcomes	• containing at least one efficacy (primary) and one safety (secondary) outcome measure: 1-primary outcomes: Neck Disability Index [NDI], pain Visual Analog Scale [VAS], Japanese Orthopedic Association [JOA] score, Odom criteria, cervical overall range of motion, superior and inferior adjacent segments range of motion. 2.secondary outcomes: blood loss, operation time, and complications (adjacent segment disease [ASD], heterotopic ossification [HO], Dural/cord injury, C5 palsy, implant subsidence, dysphagia/dysphonia, hematoma, infection)	Studies that did not report relevant outcome measures

Eligibility additional limits

1-**Study type**: Randomised Controlled Trials (RCTs) and non-randomized comparative studies that compare HS vs. ACDF in multi-level cervical disc disease will be both included in the review.

- Justification: because of insufficient RCTs to address the research question, so after discussion among review authors; non-randomized comparative studies will be included in this review together with the available RCTs.

2-**Language**: only full text in English studies will be included, reports in languages other than English will be excluded

- Justification: review team lacks proficiency in multiple languages, also to maintain consistency in data extraction and quality assessment by uniformly analyzing studies in a single language

3- **Publication**: original research articles will be included. Review articles, letters, preprints, comments, case reports, single-arm case series or conference abstracts without full text will be excluded.

5.3. Search Strategy

- **Databases**
  We will systematically search the following electronic databases from 2000 to 2024:
  1. **PubMed/MEDLINE**
  2. **Ovid (Embase)**
  3. **Cochrane Library** (CENTRAL)
  4. **Scopus**

- **Search terms**
  A combination of MeSH terms and key keywords will be used. Full search strategy will be created for each database and will be available as supplementary material file for this review. We will adapt terms to each database's indexing system. The search strategy (example for PubMed) may include:

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 (Hybrid cervical surgery OR hybrid surgery OR cervical disc
arthroplasty OR (Total Disc Replacement[MeSH Terms])

AND (Anterior cervical discectomy and fusion OR cervical discectomy
fusion OR cervical discectomy fusion OR cervical discectomy cage) OR
(diskectomy[MeSH Terms]) OR (spinal fusion[MeSH Terms])

AND ((Multilevel cervical disc degeneration OR multiple cervical disc
herniation OR cervical spondylosis) OR (Spondylosis[MeSH Terms])) OR
(Intervertebral Disc Degeneration[MeSH Terms])
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  - The exact search string will be refined with Boolean operators (AND, OR), truncation, and wildcard symbols as appropriate.
  - Filters: Abstract, Clinical Study, Clinical Trial, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial, English, Humans, Exclude preprints, from 2000 – 2024.

- **Additional Sources**
    - Reference lists of included studies and relevant review articles will be hand-searched for additional eligible articles.
    - Grey literature sources (e.g., ClinicalTrials.gov, Google scholar) may be searched if feasible.
    - Consultation of field expert is considered in our search strategy, as well as contacting of study authors for full data when required (by email to corresponding author; 2 emails with 2 weeks interval).

5.4 Study Selection Process

1. **Screening**
    - Duplicate records removal by reference manager software (EndNote) double checked with manual comparison done by first and second authors.
    - Two independent reviewers (first and second authors) will screen titles and abstracts to exclude irrelevant studies.
    - Potentially eligible full-text articles will then be retrieved for detailed assessment.
2. **Eligibility Confirmation**
    - The same two reviewers will independently apply the inclusion criteria to the full-text articles.
    - Discrepancies will be resolved by consensus or by consulting a third reviewer (the third author; professor Mahmoud Taha, head of neurosurgery department, Zagazig University, Zagazig, Egypt).
3. **PRISMA Flow Diagram**
    - We will document the selection process using a PRISMA flow diagram, detailing the number of records identified, screened, included, and excluded (**with reasons of exclusion and a full list of excluded records will be saved in a supplementary file**).

5.5 Data Extraction

- **Data Extraction Form**
    - A standardized spreadsheet on Excel software will be used to collect:
        - Study characteristics (authors, year, country, design, sample size, source of funding of each individual study).
        - Patient demographics (age, sex, diagnosis criteria, comorbidities).
        - Intervention details (levels treated, type of implants/devices used).
        - Outcomes of interest (NDI, VAS, ROM, complications, etc.).
        - Length of follow-up.
    - Two reviewers will extract data independently (first and third authors). Any disagreements will be resolved by discussion.
    - The data extraction sheet will be available as supplementary file.

5.6 Risk of Bias Assessment

- **RCTs**
    - We will use the **Cochrane Risk of Bias 2 (RoB 2)** tool to assess randomization, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases.
- **Non-Randomized Studies**
    - We will use the **ROBINS-I** (Risk Of Bias In Non-randomized Studies of Interventions) tool or **MINORS** (Methodological Index for Non-Randomized Studies) for cohort studies, as appropriate.

5.7 Data Synthesis and Statistical Analysis

1. **Qualitative Synthesis**
    - We will present a narrative summary of the included studies, focusing on key characteristics, population, interventions, and outcomes.
2. **Quantitative Synthesis (Meta-Analysis)**
    - If sufficient homogeneity is found in at least three studies reporting the same outcome with similar metrics, we will conduct a meta-analysis.
    - **Effect Measures**: Mean difference (MD) or standardized mean difference (SMD) for continuous outcomes (e.g., NDI, VAS), and risk ratio (RR) or odds ratio (OR) for dichotomous outcomes (e.g., complications).
    - **Statistical Model**: Random-effects model (DerSimonian-Laird) to account for clinical and methodological heterogeneity.
    - **Heterogeneity Assessment**: I^2 statistic and chi-square test will be used to assess heterogeneity. If $I^2 > 75\%$, we will explore reasons via subgroup or sensitivity analyses.
3. **Subgroup Analyses**
    - Where data permit, we may perform subgroup analyses based on:
        - Number of levels operated (2-level vs. 3-level).
4. **Sensitivity Analyses**
    - We will perform sensitivity analyses by excluding studies at high risk of bias or using different statistical models to evaluate the robustness of our findings.

5.8 Assessment of Publication Bias

- If 10 or more studies are included in any single meta-analysis, we will assess publication bias using **funnel plots** and tests such as **Egger's regression**.
- We will discuss the potential influence of publication bias in interpreting our findings.

5.9 Ethical Considerations

- As this study involves secondary analysis of published data, no additional ethical approval is required.
- We will adhere to established guidelines (PRISMA, Cochrane Handbook) for ethical reporting.

5.10 Dissemination of Findings

- The results will be published in a peer-reviewed journal.
- Conference presentations may be used to disseminate the findings to clinicians, researchers, and policymakers.

5.11. Funding and declaration of conflict of interest

- The authors declare that this research did not receive any external funding and they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.
- The funding details of the included primary studies will be reported in the data extraction worksheet which will be available as supplementary file.