

Review Article

Efficacy and safety of cervical cage used in patients with cervical discectomy: a meta-analysis of randomized clinical trials

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Abstract: *Background and purpose:* The efficacy and safety of cervical cage in patients with cervical discectomy and fusion was controversial in recent years. This meta-analysis was in order to evaluate the efficacy and safety of cervical cage alone. *Methods:* PubMed, Cochrane Library, EMBASE and the Clinical Trials.gov databases were searched and randomized controlled trials were included. The primary endpoint was fusion rate and the incidence of adverse events. Good to excellent rate, operation time, hospital time and blood loss were regard as secondary endpoints. *Results:* Totally, 530 patients were included from 9 RCTs. There was no difference between cervical cage and autologous bone grafts in fusion rate (RR = 0.98; 95% CI = 0.90-1.06; P = 0.60; I² = 0), good to excellent rate (RR = 1.04; 95% CI = 0.94-1.45; P = 0.47; I² = 8%) and operation time (SMD = -0.38; 95% CI = 1.70-0.94; P = 0.04; I² = 70%). There were significantly difference in the rate of adverse events (RR = 0.43; 95% CI = 0.21-0.90; P = 0.03; I² = 0), blood loss (SMD = -0.39; 95% CI = -0.74-0.05; P = 0.03; I² = 0) and hospital time (SMD = -0.32; 95% CI = -0.58-0.05; P = 0.02; I² = 0) when cervical cage compare with autologous bone grafts. *Conclusion:* No differences were demonstrated between cervical cage and autologous bone gifts respect to the fusion rate, good to excellent rate and operation time. But the cervical cage associated with lower rate of adverse events, blood loss and shorter hospital time compare with autologous bone grafts.

Keywords: Efficacy, cervical cage, cervical discectomy, meta-analysis, randomized clinical trials

Introduction

Anterior cervical discectomy with fusion is a traditional surgical technique for reduction or elimination of pain and neurological deficits caused by degenerative discs [1, 2]. A number of substrates are currently used for cervical fusion, such as cervical cage and autologous bone grafts. Cervical cages are rigid structures which are made of polymer materials or titanium that can be filled with local bone and associated with little complications [3]. The fusion rate of autologous bone grafts was 83% to 97% with common complication of bone removal such as infection, hematoma and long standing pain [4]. There are some clinical studies demonstrated that cervical cages are safe and effective in the treatment of cervical disorders and yield good long term clinical performance for patients with degenerative discs [5-8]. Despite widespread use of cervical cages, only

few clinical studies with little of sample size comparing safety and efficacy of cervical cages and autologous bone grafts in the cervical decompression and fusion procedure have been published.

Our meta-analysis was aimed to evaluate the safety and efficacy of cervical cages in order to provide evidence-based information for clinic.

Methods

In order to conduct a high-quality meta-analysis, our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [9] statement.

Data sources and searches

Cochrane Library, EMBASE, PubMed, and Clinical Trials.gov databases were searched and RCTs were included. The search time was

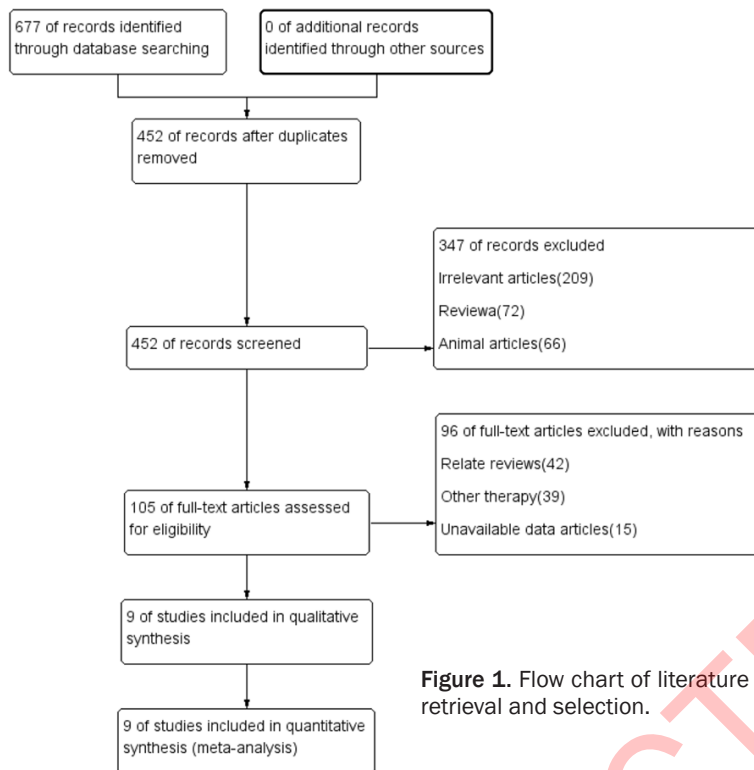


Figure 1. Flow chart of literature retrieval and selection.

was consulted to resolve conflicting opinions. The following information was extracted from the included investigations: authors' names; year of publication; characteristics of the participants; total number of participants and mean age. The fusion rate, complication rate, incidence of healed, good to excellent rate, operation time, hospital time and blood loss were extracted. In addition, information regarding random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, selective reporting, and other biases were also collected to evaluate the quality of the included investigations.

Statistical analysis

Differences in dichotomous outcomes were reported associated with the risk ratio (RR) and 95% confidence interval (CI) and continuous outcomes were reported to be associated with standard mean differences (SMDs) and 95% CI. Cochran Q test and I^2 statistic was used to assess the heterogeneity. When Cochran's $P < 0.10$ and an $I^2 > 50$, significant heterogeneity were considered to be indicative. A fixed effect model was used for pooled analyses, whereas a random effect model was used when significant heterogeneity existed. Data analyses were performed by Review Manager (RevMan) software (version 5.1; The Cochrane Collaboration, Copenhagen, Denmark). The symmetry of the funnel plot was conducted by Begger test using STATA software (version 11.1; Stata Corp LP, College Station, TX, USA). Also, sensitivity analysis was conducted by excluding each individual study through the STATA software.

Results

Search result

A total of 677 potentially publications were identified and 9 studies [10-18] were included after 87 full publications were reviewed, as shown in **Figure 1**. The baseline characteristics

set from January 1990 through June 2017. The following keywords were used in search strategies: "cervical cage"; "spinal diseases"; "cage fusion", "autologous bone grafts" and "spondylosis".

Study selection

Studies from the literature independently searched were screened by two investigators and a third investigator was consulted when disagreements arose. We included studies which met the inclusion criteria that: (1) RCTs conducted in humans; (2) Patients with spinal diseases; (3) Full-text articles of controlled trials about cervical cage used compare with autologous bone grafts published in English; and (4) The fusion rate, complication rate, incidence of healed, good to excellent rate, operation time, hospital time and blood loss were reported. Reviews, meta-analyses, editorials, observational studies, and studies in which it was not possible to assess the outcomes.

Data extraction and quality assessment

Clinical data were independently extracted by two different authors and a standardized extraction form was used. A third investigator

Table 1. Baseline characteristics of included studies

	Sample size	Mean Age	Male	Current smoker
	Cage/autologous bone grafts	Cage/autologous bone grafts	Cage/autologous bone grafts	Cage/autologous bone grafts
Singh 2016	10/10	52.3 (39-62)/49.8 (37-59)	6/7	-
Thome 2006	50/50	49±10/46±9	18/24	29/29
Hakan 2010	40/40	48 (38-59)/49 (27-70)	24/26	16/10
Benght 2007	12/12	42 (29-58)/41 (28-56)	5/6	5/5
Wigfield 2003	11/7	47.0±12.4/62.7±14.9	6/7	-
Christian 2002	36/30	50.5±13.4/47.3±11.5	27/28	11/11
Robert 2000	37/17	44.1±7.2/44.2±8.8	16/7	14/8
Saut 2007	35/30	-	24/26	-
Ludek 2002	52/51	48/47	20/25	23/20

Table 2. Results of Begger test

Endpoints	P value of Beeger test
Fusion rate	1.00
Good to excellent rate	1.00
Adverse events	0.26

including authors' names; year of publication and characteristics of the participants of the 9 included studies were shown in **Table 1**. We included 530 participants in our meta-analysis (282 for cervical and 248 for autologous bone grafts). The quality assessment was detailed in **Appendix Table 1** and **Appendix Figures 1** and **2**.

Clinical results

The fusion rate was the primary efficacy endpoint and the incidence of adverse events was the primary safety endpoint. Good to excellent rate, operation time, hospital time and blood loss were regard as secondary endpoints.

Fusion rate

Six RCTs involving 417 patients reported the fusion rate, with 222 patients randomized to the cervical cage arm and 195 randomized to the autologous bone grafts arm. No differences existed in the fusion rate between cervical cage and autologous bone grafts (RR = 0.98; 95% CI = 0.90-1.06; P = 0.60; I² = 0; **Figure 2**).

Good to excellent rate

There were 7 RCTs involving 447 patients that reported the good to excellent rate of cage fusion, with 236 patients randomized to the

cervical cage arm and 211 randomized to the autologous bone grafts arm. Cervical cage had similar results compared with autologous bone grafts with respect to good to excellent rate (RR = 1.04; 95% CI = 0.94-1.45; P = 0.47; I² = 8%; **Figure 3**).

Operation time

Four RCTs involving 411 patients reported the operation time of fusion rate. 124 patients were randomized to the cervical cage arm and 138 patients were randomized to the autologous bone grafts arm. The operation time of cervical cage and autologous bone grafts was similar (SMD = -0.38; 95% CI = 1.70-0.94; P = 0.04; I² = 70%; **Figure 4**).

Blood loss

There were 3 RCTs involving 138 patients that reported the blood loss of cervical fusion that 84 patients were randomized to the cervical cage arm and 54 were randomized to the autologous bone grafts arm. Cervical cage was associated with lower blood loss to autologous bone grafts (SMD = -0.39; 95% CI = -0.74-0.05; P = 0.03; I² = 0; **Figure 5**).

Hospital time

There were 4 RCTs involving 230 patients that reported the hospital time. There were 123 patients were randomized to the cervical cage arm and 107 were randomized to the autologous bone grafts arm. Cervical cage was associated with a significant shorter hospital time with autologous bone grafts (SMD = -0.32; 95% CI = -0.58-0.05; P = 0.02; I² = 0; **Figure 6**).

Efficacy and safety of cervical cage for cervical discectomy

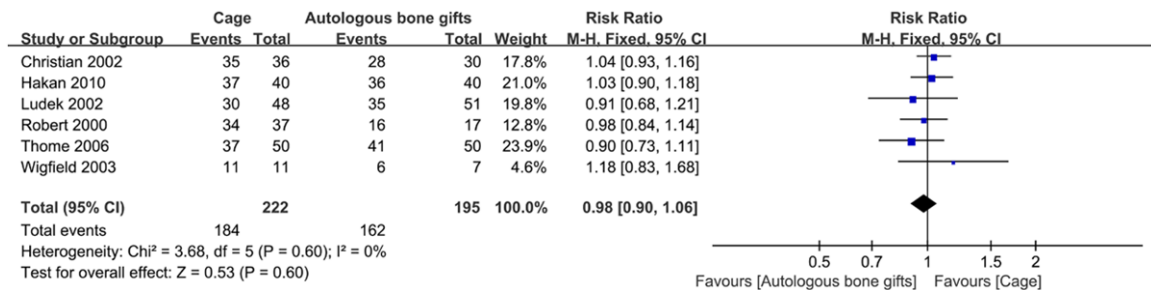


Figure 2. Forest plot of fusion rate.

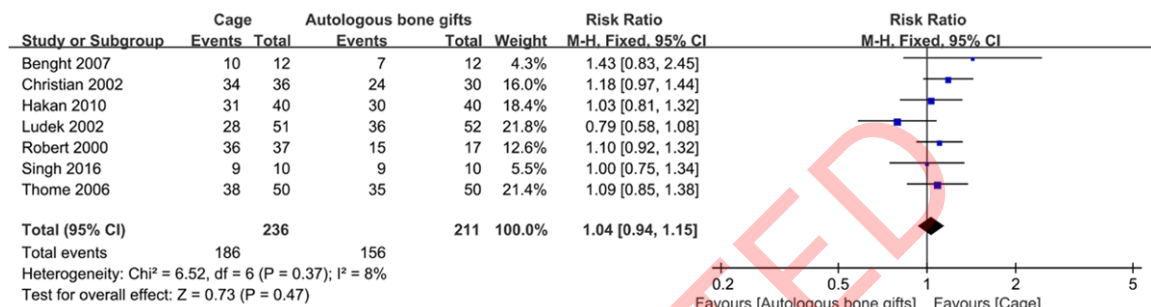


Figure 3. Forest plot of good to excellent rate.

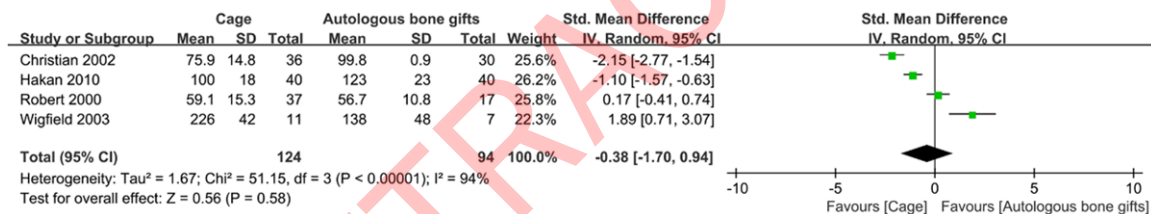


Figure 4. Forest plot of operation time.

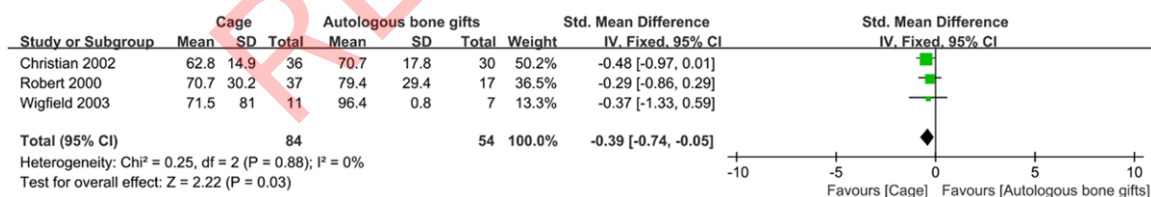


Figure 5. Forest plot of blood loss.

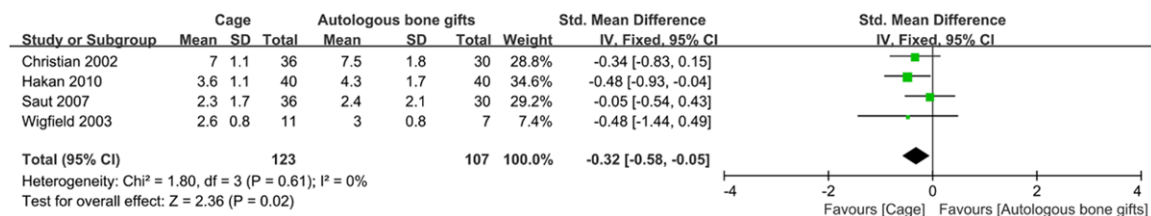


Figure 6. Forest plot of hospital time.

Efficacy and safety of cervical cage for cervical discectomy

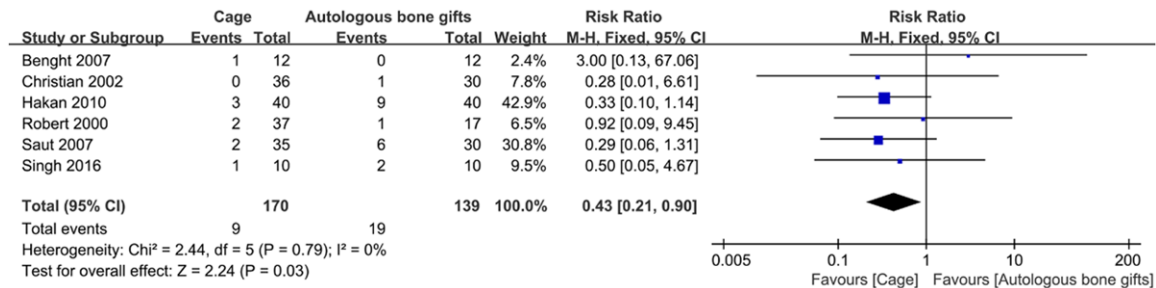


Figure 7. Forest plot of adverse events.

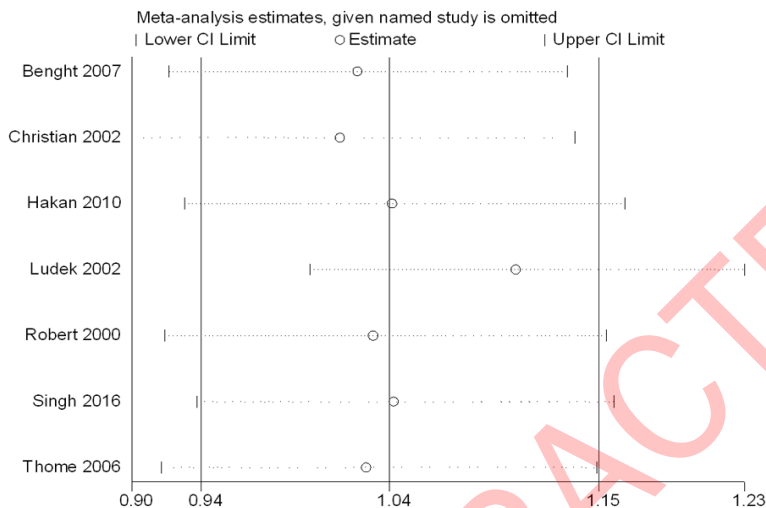


Figure 8. Sensitivity analysis.

Adverse events

The common adverse events associated with cervical cage used included infections, subsidence, displacement and bleeding. There were 309 patients included in the 6 RCTs with reported adverse events. The cervical cage associated with much lower adverse events compared with autologous bone grafts ($RR = 0.43$; 95% CI = 0.21-0.90; $P = 0.03$; $I^2 = 0$; Figure 7).

Sensitivity and publication bias analysis

Sensitivity analysis was conducted by excluding each individual study. There was no study will influence the meta-analysis results which demonstrate that our result was stable such as shown in Figure 8. No significant evidence of publication bias was obtained using the Begger test in the study endpoints, as shown in Table 2.

Discussion

This meta-analysis included 530 participants with spinal diseases randomized to cervical cage or autologous bone grafts in 9 RCTs. Based on this meta-analysis, we found that there was no difference between cervical cage and autologous bone grafts in fusion rate, good to excellent rate and operation time. But the cervical cage associated with lower rate of adverse events, blood loss and shorter hospital time compare with autologous bone grafts.

In recent years, although non-fusion techniques such as cervical disc replacement in the treatment of cervical degeneration and neuropathy caused widespread concern, but this method to improve the clinical efficacy side and the lack of sufficient evidence. Autologous bone is the only material that can combine bone-induced, bone conduction and bone regeneration, so it is recognized as the gold standard for spinal fusion material. But there still a big controversy exist in the chosen of cervical cage or autologous bone grafts. Many RCTs and retrospective analyzes found that there is no significant difference in the efficacy of the two fusion modalities in the treatment of cervical spondylosis such as pain relief and fusion rate [12, 19].

This is the newest meta-analysis about cervical cage compared with autologous bone grafts. In a meta-analysis published in 2016, which included both randomized clinical trials and retrospective studies. Compared with this met-anal-

ysis, our study only included the RCT which can enhance the reliability and evidence level, at the same, we analysis difference endpoints such as good to excellent rate and hospital time. From our meta-analysis, we found that the cervical cage associated lower blood loss compare with autologous bone grafts. This result is same as the study of Jacobs [4]. Autologous bone gifts patients with more blood loss and longer hospital time that may be the result of the large bleeding of autologous bone procedure. Addition, the quality of included studies were evaluated according to the Cochrane Handbook. In additional, detailed sensitivity and bias analysis were conducted in our study which never have been done in other publications.

There were also some limitations in our study. First, the power of our analysis was restricted because of the limit number of clinical investigations and sample sizes. Second, the differences in patient clinical management, such as the type or material of cervical cage may have affected our outcome. Finally, the quality of some evidence was discounted due to various limitations. So large RCTs associated with cervical cage are needed to further explore the efficacy and safety profile of cervical in clinical practice. Detailed subgroup analysis can be conducted when enough clinical trials published by professors in the future.

No differences were demonstrated between cervical cage and autologous bone gifts respect to the fusion rate, good to excellent rate and operation time. But the cervical cage is associated with lower rate of adverse events, blood loss and shorter hospital time as compared with autologous bone grafts.

Disclosure of conflict of interest

None.

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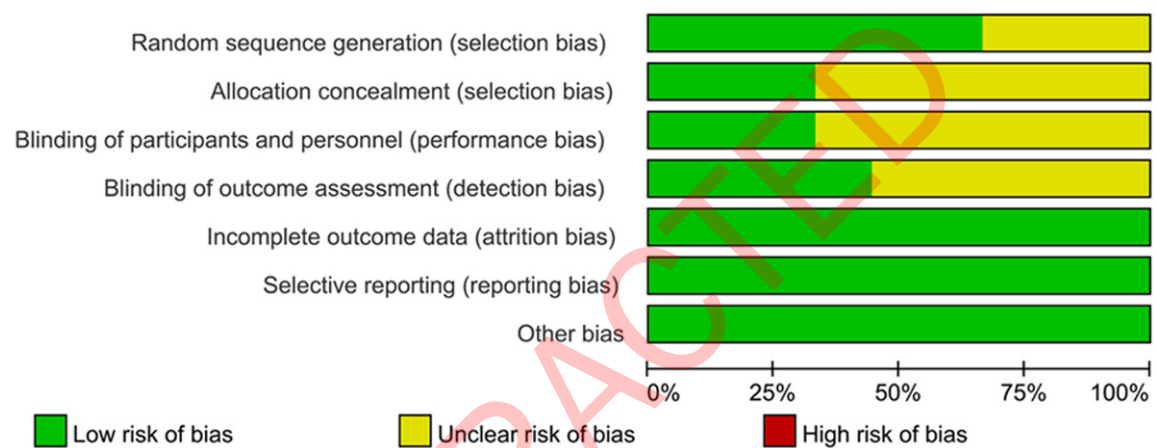
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RETRACTED

Appendix Table 1. Quality assessment of included studies

Study	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	Other bias
			Participants and personnel	Outcome assessment			
Singh 2016	Computer generated randomisation	Unclear	Unclear	Blinded	0	No	No
Thome 2006	Computer generated randomisation	Concealed list	Blinded	Blinded	0	No	No
Hakan 2010	Randomized	Unclear	Unclear	Unclear	0	No	No
Benght 2007	Randomized	Sealed envelopes	Blinded	Blinded	2 withdrew	No	No
Wigfield 2003	Centralized randomization schedule of the statistical analysis system	Sealed envelope	Blinded	Blinded	0	No	No
Christian 2002	Randomized	Unclear	Unclear	Unclear	0	No	No
Robert 2000	Randomized	Unclear	Unclear	Unclear	0	No	No
Saut 2007	Randomized	Unclear	Unclear	Unclear	0	No	No
Ludek 2002	Randomized	Unclear	Unclear	Unclear	0	No	No


Appendix Figure 1. Risk of bias graph.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Benght 2007	+	+	+	+	+	+	+
Christian 2002	+	?	?	?	+	+	+
Hakan 2010	+	?	?	?	+	+	+
Ludek 2002	?	?	?	?	+	+	+
Robert 2000	?	?	?	?	+	+	+
Saut 2007	?	?	?	?	+	+	+
Singh 2016	+	?	?	+	+	+	+
Thome 2006	+	+	+	+	+	+	+
Wigfield 2003	+	+	+	+	+	+	+

Appendix Figure 2. Risk of bias summary.