Review

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Methods of Surgical Treatment of Combined Stenosis of the Carotid and Coronary Arteries. Systematic Review

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AIM OF STUDY To determine the optimal tactics of surgical treatment of patients with combined stenosis of the carotid and coronary arteries by comparing the results of the simultaneous and staged approach according to the literature.

MATERIAL AND METHODS A systematic literature search was performed in the PubMed and MEDLINE databases to compare the results of simultaneous and staged interventions for combined stenosis of the carotid and coronary arteries. The following keywords were used as a search query: ("combined coronary and carotid artery stenosis and simultaneous"), ("combined coronary and carotid artery stenosis and staged"), ("combined coronary and carotid artery stenosis and cost"). We compared the results of simultaneous (interventions on the vessels of both systems are performed simultaneously) and staged operations (interventions are performed alternately, with a time interval from 2 to 160 days). References from included studies were also manually reviewed. The search was conducted by two independent experts (S.L., S.N.), and any disagreement was resolved by the clinical expert (A.A.).

RESULTS A literature search identified 198 potentially relevant studies. A total of 13 studies met the inclusion criteria, of which 5 included two interventions. This systematic analysis includes the results of treatment of 43,758 patients with combined stenosis of the carotid and coronary arteries, who underwent staged or simultaneous revascularization of the vessels of the carotid and coronary flow.
Perioperative neurological complications in the group of staged operations were observed somewhat more often than in the group of simultaneous interventions (3.2% versus 4.22%; p=0.8), myocardial infarction was observed with a frequency of 1.5% in the group of simultaneous interventions, and 2.5% (p=0.5) in the group of staged interventions. The mortality rate after simultaneous and staged interventions was 3.9% and 3.6%, respectively, with a fairly high spread in the study groups (p=0.5). Data analysis showed that simultaneous interventions did not affect the incidence of neurological, cardiac complications, and deaths (OR (odds ratio) 1.02; 95% CI (confidence interval) — 0.98–1.14, p = 0, 69; OR — 1.26; 95% CI — 0.66-2.41; p=0.48; and OR — 0.97; 95% CI — 0.67-1.38; p=0.85 — respectively).

CONCLUSION 1. The cumulative incidence of neurological and cardiac complications and mortality in staged tactics, according to observational studies included in this systematic review, is 4.2%; 2.6% and 3.6%, respectively (p>0.05). 2. The cumulative incidence of neurological and cardiac complications and mortality with simultaneous tactics according to observational studies included in this systematic review is 3.3%; 1.5% and 3.9%, respectively (p>0.05). 3. Given the relatively low risk of developing myocardial infarction (OR — 1.26; 95% CI — 0.66–2.41; I2 — 94%), the low risk of developing neurological complications (OR 1.02; 95% CI — 0,98–1.14; I2=75%), and deaths (OR — 0.97; 95% CI — 0.67–1.38; I2 — 76%) — (p>0.05), with simultaneous interventions, it can be concluded that simultaneous interventions may be the method of choice for surgical treatment for combined stenosis of the carotid and coronary arteries.

Keywords: stenosis of carotid arteries, stenosis of coronary arteries, simultaneous surgery, staged surgery

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CABG – coronary artery bypass grafting
CI – confidence interval
LMCA – left main coronary artery
OR – odds ratio
CA – carotid arteries

INTRODUCTION

Coexisting of carotid artery stenosis and ischemic heart disease occurs in 11–20% of patients and in 2–11% of patients it is often accompanied by a stroke in the postoperative period after coronary artery bypass grafting (CABG). In some cases, this complication is followed by disability and death [1, 2]. The decision to perform interventions in different arterial regions is often made based on the experience of the surgical team. Current recommendations do not cover this problem in sufficient detail, and in recent reviews and meta-analyzes there are no unambiguous conclusions in favor of one or another approach [3, 4]. According to a number of studies, the incidence of perioperative stroke was the same when reconstructive carotid artery (CA) surgery and CABG were performed simultaneously, or if CABG was preceded by reconstructive CA surgery [5]. The incidence of stroke increased significantly if carotid endarterectomy was performed in the first stage. However, the incidence of myocardial infarction and mortality turned out to be higher when CABG preceded the restoration of blood flow in the CA. The pathogenetic reliability and clinical efficacy of surgical treatment of hemodynamically significant lesions of the brachiocephalic and coronary arteries have been proven in a number of studies.

This systematic literature review covers publications analyzing approaches of surgical treatment for concomitant carotid and coronary stenoses. The study included works published from 2000 to 2019 inclusive. **Aim of study:** To determine the optimal tactics for surgical treatment by comparing the outcome of simultaneous and staged methods in patients with concomitant carotid and coronary stenoses mentioned in the literature.

To achieve this goal, we have identified the following tasks:

1. To assess the incidence and risk of developing neurological and cardiac complications and mortality for the staged treatment.

2. To assess the incidence and risk of developing neurological and cardiac complications and mortality for the simultaneous approach.

3. To determine the optimal tactics of surgical treatment for concomitant carotid and coronary stenoses.

MATERIAL AND METHODS

SELECTION CRITERIA

The study included randomized, cohort, controlled, or observational studies that met the following criteria: (1) patients with concomitant coronary and carotid artery stenoses; and (2) comparison of simultaneous and staged variants of surgical coronary and carotid artery revascularization. Review and editorial articles in languages other than Russian and English were excluded. Also, repeated or duplicate publications were excluded from the study (Fig. 1).

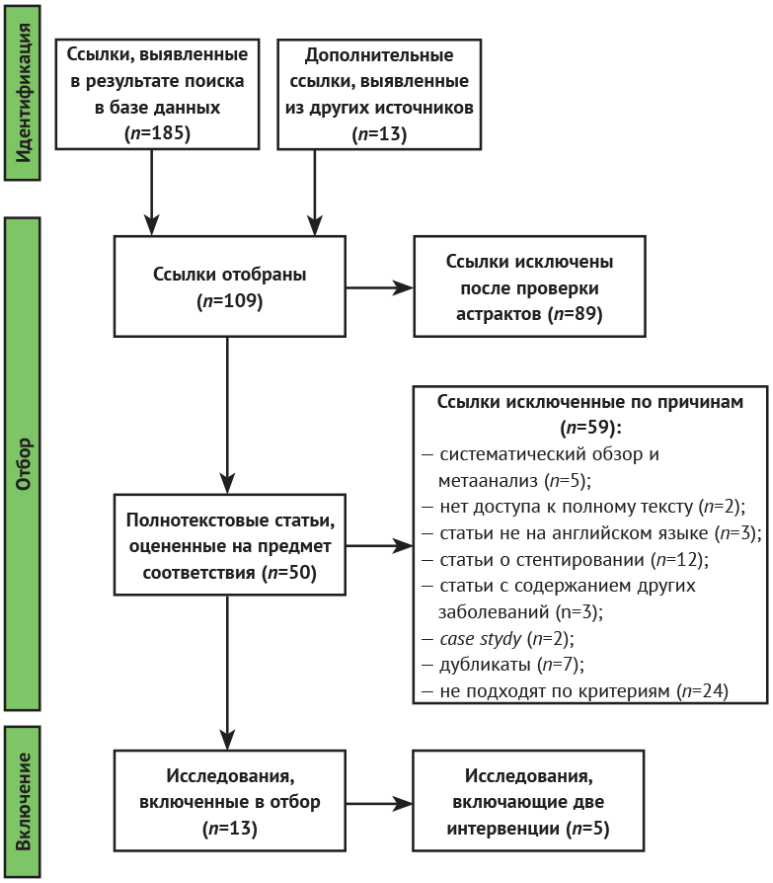

Fig. 1. The diagram describing selection criteria for meta-analysis

SEARCH STRATEGY

Literature searches were performed using Pubmed, MEDLINE and EMBASE to identify relevant articles from 2000 to 2019 inclusive. The search terms used were as follows: carotid artery stenosis; ischemic heart disease; coronary artery bypass grafting; and carotid endarterectomy. Also, as search queries we used the following phrases: “concomitant coronary artery and carotid artery stenosis”; “simultaneous / synchronous” and “staged” in combination with “coronary artery revascularization”, “carotid artery revascularization”. To avoid data loss, we also used manual search approaches with the above criteria in mind.

During meta-analysis we initially looked at baseline patient characteristics to determine the homogeneity of the studies presented for analysis. Mortality, incidence of myocardial infarctions and strokes in the early postoperative period (up to 30 days after surgery) were the main “endpoints” of our meta-analysis; we did not take into account data concerning long-term outcomes.

The search strategy was adopted in accordance with the criteria given in the MOOSE reporting guidelines for Meta-analyses of Observational Studies [6, 7]. Disagreements were resolved by consensus. Data was extracted from articles using predefined data selection forms. The quality of the included studies was assessed using the Newcastle – Ottawa scale [8].

STATISTICAL ANALYSIS

All statistical analyses were performed using Stata 12.0 (Stat-Corp, College Station, TX) and Review Manager 5.3 software. The main incidence rates for the studied endpoints were obtained with the help of R package meta using Freeman-Tukey variance stabilizing arc-sine transformation method [9]. Early mortality was reported as the hazard ratio with the 95% confidence interval (CI). To assess the fixed or random effects (where applicable), we resorted to the inverse variance method [7]. Estimating total measurement variation, we used the I2. To assess heterogeneity, sensitivity analysis and cumulative meta-analysis were also performed. The p-value less than 0.05 was applied as a significance level using 95% CI.

RESULTS

During the search, 198 publications were found, of which 108 articles were selected taking into account the availability of the full version of the article and the language of writing (English / Russian). Further, 49 articles that did not have full-text versions were excluded from the analysis. 54 articles, in full-text format, were assessed for the compliance with the selection criteria, and then 19 publications describing vascular stenting or open heart interventions (5) were rejected. Also, review articles (5) and articles published in languages other than Russian and English (2) were excluded from the final analysis. The final analysis included 5 publications that fully met all the search requirements (Table 1).

Table 1

Research characteristics

Author	Year	Study duration	Number of patients
Hempe S.	2018	5 years	323
Feldman D.	2017	9 years	21 699
Prasad S.M.	2010	5 years	21 489
Chiappini B.	2005	n/d/a	202
Khadzhibayev A.M.	2019	4 years	45

Note: n/d/a — no data available

Thus, the study included data of 43,758 patients with concomitant carotid and coronary stenoses; simultaneous revascularization was performed in 21,601 patients (49.36%), in the remaining 22,157 cases (50.64%) patients underwent staged surgical interventions (direct staged or reverse staged procedures). Baseline patient characteristics are presented in Table 2.

Table 2

Baseline patient characteristics

Author	Number of patients		Left main coronary artery stenosis		Emergency admission		Symptomatic carotid stenosis	
	Simultaneous	Staged	Simultaneous	Staged	Simultaneous	Staged	Simultaneous	Staged
Chiappini B.	140	62	42	10	40	12	40	15
Feldman D.N.	15 402	6297	n/d/a	n/d/a	7224	3432	297	321
Hempe S.	307	16	n/d/a	n/d/a	n/d/a	n/d/a	49	3
Prasad S.M.	5732	15757	2130	6238	n/d/a	n/d/a	n/d/a	n/d/a
Khadzhibayev A.M.	20	25	n/d/a	n/d/a	n/d/a	n/d/a	15	14

Note: n/d/a — no data available

The median patient age in the group of simultaneous interventions was 68.5 ± 0.9 years, in the group of staged interventions: 66.7 ± 2.8 years; females were 30.73% and 33.4%, respectively. These parameters were not statistically significant. Table 3 shows cumulative patient baseline parameters included in the study.

Table 3

Cumulative patient baseline parameters

Parameters	Simultaneous approach	Staged approach
Number of patients	21 601 (49,36%)	22 157 (50,64%)
Median age	68,5	66,7
Female gender	6637 (30,73%)	7409 (33,44%)
Left main coronary artery stenosis	2172 (36,99%)	6248 (39,5%)
Emergency admission	7248 (46,8%)	3455 (54,1%)
History of transient ischemic attack / stroke	400 (2,5%)	354 (5,5%)

Symptomatic carotid artery lesions were detected in 400 (2.5%) and 354 patients (5.5%) from the simultaneous and staged groups, respectively. Differences in the structure of coronary artery lesions were also not statistically significant; left main coronary artery (LMCA) stenosis was diagnosed in 2172 (36.99%) and 6248 (39.5%) patients operated simultaneously or in stages, respectively.

The difference in the primary combined outcomes was also statistically insignificant. Table 4 summarizes the outcomes of staged and simultaneous surgical treatment for concomitant carotid and coronary stenoses.

Table 4

Perioperative results of surgical revascularization of combined stenoses of the carotid and coronary arteries

Authors	Number of patients	Neurological complications		Cardiac complications		Mortality	
		Simultaneous	Staged	Simultaneous	Staged	Simultaneous	Staged
Chiappini B.	202	9 (6,43%)	3 (4,84%)	2 (1,43%)	2 (3,23%)	9 (6,43%)	8 (12,9%)
Feldman D.N.	21699	293 (1,9%)	176 (2,79%)	n/d/a	n/d/a	585 (3,8%)	277 (4,4%)
Hempe S.	323	16 (5,21%)	0 (0%)	5(1,63%)	0(0%)	13 (4,23%)	1 (6,25%)
Prasad S.M.	21489	390 (6,8%)	754 (4,79%)	n/d/a	n/d/a	235 (4,1%)	507 (3,22%)
Khadzhibayev A.M.	45	1 (5%)	1 (4%)	n/d/a	n/d/a	1 (5%)	n/d/a

Note: n/d/a — no data available

As you can see from Table 4, the incidence of neurological and cardiac complications in different studies varied. Thus, the lowest rates of neurological complications were observed in the study by *Feldman D.N. et al*., where their value for simultaneous surgeries was 1.9%, and for staged surgeries: 2.79%.

Cardiac complications (including perioperative myocardial infarction) were analyzed by three groups of researchers: according to *Chiappini B. et al.,* the incidence of such complications in simultaneous interventions was lower (1.43%) than in staged ones (3.23%); while in the research by *Hempe S*., the incidence of myocardial infarction was higher in simultaneous interventions (1.63%) than in staged ones (0%). Cumulative mortality rates and cumulative incidence of complications after surgery are presented in Table 5.

Table 5

Cumulative indicators of treatment outcomes

Parameters	Surgery		*p*
	Simultaneous	Staged	
Neurological complications	709 (3,28%)	934 (4,2%)	0,8
Cardiac complications	7 (1,5%)	2 (2,56%)	0,5
Mortality	843 (3,9%)	793 (3,58%)	0,5

It should be noted that in the group of staged interventions the incidence of combined neurological complications (stroke, transient ischemic attack) was higher than in the group of simultaneous interventions: 709 (3.28%) and 934 (4.22%), respectively (p = 0.8) (Fig. 2).

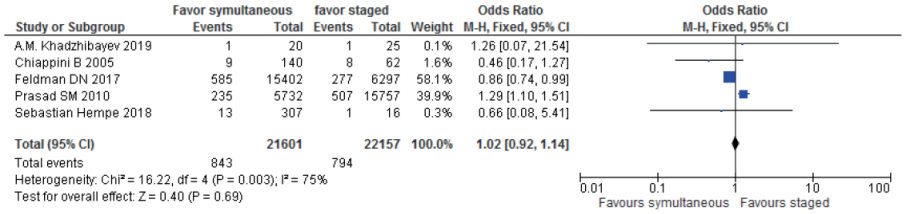

Fig. 2. Forest plot showing the risk of developing neurological complications during simultaneous and staged interventions

In the studies by *Prasad S.* and *Khadzhibayev A.M.* the risk of developing neurological complications was 1.29 and 1.26, while in the works by *Chiappini B., Hempe S.* and *Feldman D.*: 0.46; 0.66 and 0.86, respectively. The relative cumulative risk of stroke in simultaneous interventions was slightly lower than in staged interventions (odds ratio (OR): 1.02; 95% confidence interval (CI): 0.98–1.14; I2 = 75%), but the parameter did not reach statistically significant values.

It should be noted that a different trend was observed in relation to combined cardiac complications (Fig. 3).

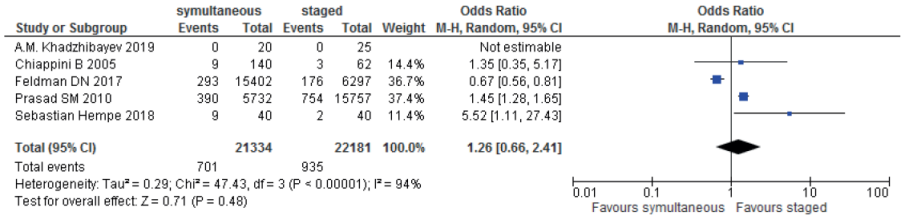

Fig. 3. Forest plot showing the risk of developing cardiac complications (myocardial infarction)

In the studies by *Chiappini B., Prasad S.* and *Hempe S.,* the risk of developing cardiac complications was higher and amounted to 1.35; 1.45 and 5.52, respectively, while in the research by *Feldman D.*: 0.67, and in the study by *Khadzhibayev A.M.* such complications were not noted at all. Thus, the cumulative incidence of myocardial infarction was lower in simultaneous interventions: 1.5%, compared to staged interventions: 2.56%, (OR: 1.26; 95% CI: 0.66–2.41; I2= 94%). However, given the low statistical significance (p = 0.9), talking about the advantage of one method over the other is not justified

Mortality was noted in the group of simultaneous interventions a little more often (Fig. 4).

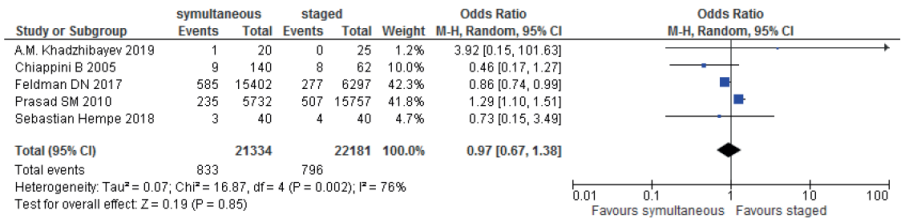

Fig. 4. Forest plot showing the mortality risk for simultaneous and staged interventions

In two studies, simultaneous interventions were accompanied by a higher risk of death (*Prasad S.* and *Khadzhibayev A.M.*: 1.29 and 3.92, respectively), although in the study by *Khadzhibayev A.M.*, pulmonary complications were the cause of death. Thus, the cumulative mortality in the group of staged interventions was 3.58%, while in simultaneous surgeries it was 3.90%, but the revealed difference was not statistically significant, which manifested itself in a relatively low risk of deaths (OR: 0.97; 95 % CI: 0.67-1.38; I2= 76%).

Based on the above graphs, it can be concluded that simultaneous and staged interventions for concomitant carotid and coronary stenoses are not accompanied by a statistically significant difference in primary composite outcomes, such as neurological, cardiac complications and mortality.

DISCUSSION

The choice of the optimal surgical approach to patients with concomitant carotid and coronary stenoses still gives rise to much controversy. To date, there has been no level 1 evidence for practical work. It should be noted that most patients with carotid artery stenosis have varying severity of coronary artery disease, but the vast majority of patients may undergo staged intervention based on clinical priority. Therefore, in practice, only a small number of patients can require a decision regarding staged or simultaneous intervention.

In the era of evidence-based medicine, a randomized multicenter study would solve this problem, but in practice, planning and carrying out such a study involves many practical, theoretical and logistic challenges. Thus, if we compare with previous meta-analyzes and systematic reviews, then the review by *Naylor A.R. et al.* (2003) lists only 5 randomized multicenter studies, which for staged interventions were accompanied by a mortality rate of 5.8%; 8.2%; 10.7%; 13.0% and 16.9%, respectively. Whereas in our systematic review, only 2 randomized multicenter studies (data from 2000 to 2019) can be noted, where mortality for staged interventions was 4.4% and 3.2%, respectively [2, 10].

It should be noted that the parameters did not undergo significant changes in comparison with the data of 2003, with the exception of the incidence of myocardial infarction, which in the perioperative period decreased from 3.6 to 1.57% and from 6.5 to 2.56% in the simultaneous and staged groups, respectively. Although it should be noted that during the specified period (2000–2019), 13 studies were conducted that analyzed data from simultaneous interventions [11–22, 23], 5 publications contained comparison groups for simultaneous / staged surgeries [2, 5, 24–26] and only 3 studies analyzed the data of staged surgical treatment for concomitant carotid and coronary stenoses, and this indicates that more aggressive approaches are becoming more popular [27-29].

It is rather difficult to assess the true risk of stroke in the early postoperative period, primarily because the majority of centers performing preoperative screening examinations of carotid arteries, as a rule, advocate simultaneous intervention in patients with more pronounced clinical manifestations of carotid or coronary artery disease. In a recent systematic review [5], 41.1% and 43.1% of patients in the simultaneous and staged groups, respectively, had symptomatic carotid artery stenosis. In this case, 36.8% and 30.5% of patients in the simultaneous and staged groups, respectively, had bilateral carotid artery stenosis. LMCA stenosis was diagnosed in 24.7% and 27.5% of patients, while emergency CABG was performed in 39.1% and 28.9% of patients in the simultaneous and staged groups, respectively. In the present study, the distribution of patients with carotid and coronary artery lesions was more dramatic: symptomatic carotid artery stenosis was diagnosed in 2.5% and 5.5%; LMCA stenosis was observed in 36.9% and 39.5%; and emergency intervention was required in 46.8% and 54.1% of patients in the groups of simultaneous and staged interventions, respectively ($p \geqslant 0.1$).

CONCLUSIONS

Based on the foregoing, we can conclude that there is no systematic evidence of the advantages of one strategy over the other with the same clinical data.

1. The cumulative incidence of neurological and cardiac complications and mortality rate in the staged approach, according to observational studies included in this systematic review, is 4.2%; 2.6% and 3.6%, respectively ($p > 0.05$).

2. The cumulative incidence of neurological and cardiac complications and mortality rate in simultaneous approach, according to observational studies included in this systematic review, is 3.3%; 1.5% and 3.9%, respectively ($p > 0.05$).

3. Considering the relatively low risk of developing myocardial infarction (OR: 1.26; 95% CI: 0.66–2.41; I2= 94%), the low risk of developing neurological complications (OR: 1.02; 95% CI: 0.98 -1.14; I2 = 75%), and deaths (OR: 0.97; 95% CI: 0.67-1.38; I2 = 76%) - ($p > 0.05$) in simultaneous interventions , it can be concluded that simultaneous approach can be the choice of surgical treatment for concomitant carotid and coronary stenoses.

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