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## Clinical Research Article

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# Prophylactic measures to prevent cerebral oxygen desaturation events in elective beach-chair position shoulder surgeries: a systematic review and meta-analysis

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**Background:** Prophylaxis for cerebral desaturation events (CDEs) during anesthesia in the beach chair position (BCP) for shoulder surgeries has not been evaluated. We systematically analyzed the effectiveness of various prophylactic measures used in this clinical setting.

**Methods:** We performed a meta-analysis (PROSPERO; no. CRD42020167285) of trials reporting CDEs and regional cerebral oxygen saturation ($rSO_2$) and jugular venous oxygen saturation ($SjvO_2$) values in anesthetized patients undergoing shoulder surgery in BCP. Considering the type of prophylactic measures used (pharmacological or non-pharmacological), a subgroup analysis was planned. Outcomes included (1) $rSO_2$ and $SjvO_2$ data with and without prophylactic measures for CDEs, recorded for different time intervals, and (2) the number of patients experiencing CDEs and hypotension.

**Results:** Twelve studies (786 patients) were included in the analysis. We observed lower absolute $rSO_2$ values for early and all-time periods for vasoactive agent prophylaxis. The lowest achieved $rSO_2$ values were also lower for vasoactive agent prophylaxis. Risk of CDEs was higher with vasoactive agent prophylaxis. Subgroup analysis identified targeted mild hypercarbia as effective in preserving cerebral oxygenation. Similarly, targeted mild hypercarbia prevented the fall in $rSO_2$ with position change. Meta-regressions revealed statistically significant highest estimates for vasoactive agent prophylaxis in contrast to targeted mild hypercarbia. Likelihood of not developing CDEs was higher for targeted mild hypercarbia. In contrast to $rSO_2$, most prophylactic methods reduced hypotensive episodes.

**Conclusions:** Targeted mild hypercarbia can reduce BCP-related CDEs. Evidence does not favor prophylactic use of vasoactive agents for the prevention of cerebral desaturations irrespective of whether their use interferes with cerebral oximetry readings.

**Keywords:** Arthroscopy; Oximetry; Prophylaxis; Randomized controlled trial; Shoulder; Sitting position; Statistics; Systematic review.

## Introduction

Beach chair position (BCP) surgeries are associated with significant cerebral desaturation events (CDEs) in as many as 80% of patients [1,2]. Cerebral oxygenation is depen-

dent on a combination of multiple factors such as cerebral blood flow (CBF), mean arterial blood pressure (MAP), partial pressure of oxygen, cardiac output, and hemoglobin levels. A reduction in MAP during anesthesia in BCP may decrease the CBF [3–5]. A strong association of the hypotensive response with decrease in regional cerebral oxygen saturation ($rSO_2$) and jugular venous oxygen saturation ($SjvO_2$) has been observed [6–8]. In such situations, pharmacological agents such as ephedrine and phenylephrine, which rapidly increase MAP, are frequently used to obtain indirect benefits on cerebral oxygenation. Alternatively, prophylactic measures have been successfully used to prevent CDEs, including non-pharmacological techniques such as preloading with crystalloids/colloids or the use of sequential compression devices (SCDs) [9–11]. Vasoactive agents administered prophylactically can theoretically achieve a rapid increase of MAP and consequently the increase of CBF, however, the decline observed in $rSO_2$ suggests otherwise [12]. The association between the use of prophylactic compression stockings and reduced occurrence of CDEs is unclear, as similar incidences were also reported in patients with their use [13]. We could not find any analysis of pooled data in the available literature to support or refute this association.

Our study attempted to determine whether any particular pharmacological or non-pharmacological technique is useful for reducing CDEs during BCP surgeries. Confirming an association between the two would improve predictability, provide insight into the possible underlying pathophysiological mechanisms, and guide the anesthesiologist on the most efficacious method of preventing these undesirable events. Therefore, we performed a systematic review and meta-analysis to summarize the existing evidence on the ability of prophylactic measures to prevent CDEs in this clinical setting.

## Materials and Methods

### Registration and protocol

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses [14] and was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO, no. CRD42020167285).

### Eligibility criteria

We included prospective randomized clinical studies or randomized controlled trials (RCTs) with adult patients (> 18 years) who underwent elective shoulder surgeries in BCP. Reporting of monitored cerebral oxygen saturation-related data and at least one

prophylactic method used to prevent CDEs were mandatory for inclusion. Publications in all languages were considered. The patients received one of the following anesthetic modalities: (1) planned general anesthesia (GA) or (2) regional anesthesia (RA), *viz* interscalene brachial plexus block or similar block in combination with GA. We excluded studies wherein patients underwent surgeries under RA alone, at < 45° BCP, or with American Society of Anesthesiologists physical status > 3.

### Information sources

An electronic literature search, specifically restricted to randomized studies or RCTs of BCP, was conducted in MEDLINE, CINAHL (EBSCO host), Google Scholar, and the Cochrane Central Register of Controlled Trials. The bibliography of the retrieved manuscripts was searched for additional studies pertaining to data encompassing our primary outcome of interest. These included studies reporting incidence of CDEs, maximum and minimum average cerebral oxygen saturations, serial average cerebral saturation values overtime periods, critical CDEs, and the percentage change of cerebral saturations, with a caveat that both supine, pre-BCP and BCP data are available. Similar to cerebral saturation, $SjvO_2$ was documented whenever data were available. Twenty-first-century literature, that is, literature published only after January 1, 2000, was scanned because anesthesia protocols have remained uniform during this period. Cohorts with matched controls, retrospective studies, reviews with inadequate information on primary outcomes of interest, abstracts, and letters to the editor were not included. The detailed search strategy is shown in Supplementary Material 1, which depicts the keyword-based search inclusion terms.

### Study selection and data collection

A collection of studies was conducted by TPT and HK. The manuscripts meeting the inclusion criteria were assessed, and data were extracted following a standardized format by the same authors. The extracted items comprised study characteristics, risk of bias domains [15], participant disposition, and study outcomes. The PICO inclusion criteria comprised the following elements, focusing on patients, interventions, comparisons, and outcomes, and were used to identify components of clinical evidence. Patients who underwent shoulder surgery under anesthesia in BCP with cerebral oxygen saturation monitoring using any type of cerebral oximetry device were considered. They were categorized according to the type of surgery or anesthesia, number of patients, the position adopted for surgery, and monitoring for CDEs. Inter-

ventions referred to prophylactic measures used to prevent CDEs. These patients must have had at least one type of prophylactic method to prevent cerebral desaturation in the sitting position. With regard to the type of intervention, study authors could consider any type of pharmacological or non-pharmacological method deployed before the CDE. The comparison of variables was between 'with and without' prophylactic measures. This is an alternative to intervention–placebo, different drugs, measures, or therapy. Outcomes were classified as primary or secondary. The former included cerebral oxygen (de)saturation data with and without the use of prophylactic measures at various time intervals using $rSO_2$ and $SjvO_2$ cerebral oximetry values. The latter included the incidence of CDEs and hypotension episodes, associations with MAP, and the use of vasoactive agents with CDEs.

## Data synthesis and analysis of outcomes

Data relevant to the outcomes of interest were extracted from each study in this meta-analysis. The $rSO_2$ or $SjvO_2$ data included continuous data documented as pooled averages or sequential data at various intervals for a study. Data were collected as a single or combined value in the form of mean and standard deviation (SD) or median and interquartile range (IQR), respectively. If multiple datasets were available, they were converted into pooled statistical averages. The other dichotomous data included the number of patients experiencing CDEs.

The data were tabulated before induction (baseline) and post-induction (relating to pre-BCP and BCP categories after stabilization of vital signs). The BCP $rSO_2$ or $SjvO_2$ data were pooled for the time periods mentioned in the respective publications. If the recorded data timings were non-specific, they were approximated to a specific time by a mutual discussion with the authors. Publications with unreported or inconclusive data that could not be obtained after attempts to contact the authors were excluded from this review.

To analyze cerebral saturation data, four categories of $rSO_2$ or $SjvO_2$ values were considered from the study (i.e., prophylactic measures used) and control (i.e., no prophylactic measures used) groups. The absolute values, which are mentioned as percentages, for both groups with respect to time (i.e., early or entire period of BCP) or for the type of outcome studied (i.e., $rSO_2/SjvO_2$) were recorded. These data were synthesized as pooled data that included (1) the early BCP period ($rSO_2/SjvO_2$ values, for immediate, the first 15 min of BCP), (2) the entire BCP period (all-time overall $rSO_2/SjvO_2$ values, until the reported time period or the end of surgery) referring to the pooled average values of those at all time points during BCP, (3) the lowest observed at BCP $rSO_2/SjvO_2$

values. When the right and left cerebral hemispheres were monitored separately (with either single or two different methods), the lowest value was included (4) the baseline values, which refer to the supine, pre-BCP $rSO_2$ values after induction of anesthesia.

The data presented in tables, text, and images were used as the primary sources for extraction. Graph digitizing software (Engauge Digitizer version 10.10, @Mark Mitchell) was used to efficiently extract and estimate raw numerical data whenever textual numerical data were unavailable. When range and IQR were available, SD was estimated using the formulas SD = range / 4 and SD = IQR / 1.35, as described by the Cochrane Handbook for Systematic Reviews of Interventions [16]. Data are reported as 95% CI. The median value was used to estimate the mean if the value was not reported. Whenever the standard error of the mean (SEM) was reported, SD was obtained as SD = SEM × $\sqrt{N}$ [16]. To account for drop-out cases over time or termination of BCP before the time specified in the meta-analysis, patient numbers were approximated to the nearest values for pooled data estimation. If the exact time point was not specified in the manuscript, then the approximated time point was considered by the authors' judgment.

Individual definitions for CDEs and hypotension were accepted as described by each study. Dichotomous data such as the occurrence of CDEs and hypotension were converted into incidence (*n/N*) for early and overall time periods. All analyses were performed assuming no incidences of CDEs in the supine position under anesthesia. CDE occurrence was counted whenever the event was reported at least once, based on the original study authors' definitions. Complications were analyzed on an 'intention to treat' basis since in some subgroups, patients were repositioned back to supine following BCP-induced hemodynamic disturbances or CDEs [17].

With regard to MAP, data evaluation and synthesis were similar to those applied for CDEs or $rSO_2/SjvO_2$ values. The incidence of hypotension was counted whenever the events were reported at least once either individually or sequentially for each patient.

## Pre-defined sources of heterogeneity

To explore the potential causes of heterogeneity that could influence the primary outcomes, we pre-identified certain aspects of individual study groups. These included (1) anesthetic technique (GA vs. combined GA and RA); (2) induction agent (propofol vs. thiopentone); (3) maintenance anesthetic agent (propofol vs. inhalational agents); (4) prophylactic measures (vasoactive agents vs. preloading vs. SCD vs. targeted mild hypercarbia techniques vs. compression stockings vs. others), and (5) maintenance vasopressors (phenylephrine vs. ephedrine vs. others).

Meta-analysis was conducted using Review Manager (RevMan 5.4.1, Cochrane Collaboration, Denmark, 2014). A random-effects model was used for all analyses. Heterogeneity was measured and expressed as $I^2$. For continuous variables (rSO$_2$/SjvO$_2$), mean differences (MDs) were compared using the inverse-variance (I-V) method. For dichotomous variables (incidence of CDEs and hypotension), odds ratio (OR) or risk ratio (RR) was computed using the Mantel-Haenszel (M-H) or I-V method. Natural log transformation was adopted [18], as the outcomes for incidences were expected to be non-normally distributed.

### Meta-regression analysis

Because of overlapping of use (i.e., more than one) of different prophylactic measures, a meta-regression analysis was planned to estimate the effectiveness of the individual prophylactic measures. Pre-BCP (supine, after anesthesia induction) and BCP (all-time overall, absolute [%], and pooled) cerebral saturation values were considered for meta-regression. Meta-regression data inputs were different from the data of conventional meta-analysis, where the former included the MDs from baseline to all-time overall fall of rSO$_2$ values. Meta-regression was performed using JASP software (Version 0.9.2, BibTeX, University of Amsterdam, the Netherlands). The effect size (estimate) and standard error (SE) were used for meta-regression. *A priori* defined prophylactic measures were used across the study groups. We included all prophylactic measures that were identified among study groups, such as compression stockings, SCDs, targeted mild hypercarbia, crystalloid loading, hydroxyethyl starch (HES), regional ischemic preconditioning technique (RIPC), and vasoactive agents for meta-regressions. Meta-regressions were also performed for 'the number of patients experiencing CDEs', in which baseline supine, pre-BCP CDEs were assumed as 'zero' for the analysis. All meta-regressions were performed using the restricted maximum likelihood method and random effects. An omnibus test of the model coefficients and tests for heterogeneity were used for the model. Simultaneous to Egger's regression tests for funnel plot asymmetry evaluations, a visual inspection of the funnel plot was carried out to rule out publication bias. The influence of such studies on the model was also assessed. The parameter covariance was assessed for the combined effects of prophylactic measures. Statistical significance was set at P < 0.05 (2-tailed).

### Grading of Recommendations Assessment, Development and Evaluation

The certainty of the evidence was summarized using the Grad-ing of Recommendations Assessment, Development and Evaluation (GRADE) [19] approach for individual outcomes. The strength of recommendations reduces the potential to facilitate critical appraisal and improves the communication of judgments. GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, 2020 [developed by Evidence Prime, Inc.]) was used to facilitate the development of evidence summaries and recommendations.

## Results

### Literature identification and study characteristics

From 2,297 studies that were initially screened, 56 potentially relevant manuscripts were selected based on abstracts (Supplementary Material 2). Of these, 12 trials provided the data for analysis (Supplementary Material 3) [7,13,20–29] including Jadad scores. Data from 786 patients were included in the analysis.

Cerebral oxygenation monitoring was performed using INVOS™ 5100 B/C (Medtronic, Ireland) cerebral oximetry monitoring devices [7,13,20–27,29] (near-infrared reflectance spectroscopy) in all included studies in this review, except in a single study [28] in which the FORE-SIGHT™ device (Edwards Lifesciences, USA) was used. All the studies reported baseline data with respect to rSO$_2$ including pre- and post-induction values, except for a single study [24] in which only the mean (SD) maximum fall of cerebral saturation values was reported. The physiologic principles to prevent CDEs followed in each included study, however, were dissimilar. Because rSO$_2$ values can be affected by a variety of factors, the mechanisms used by the authors in the prevention of falls in rSO$_2$ varied. Vascular tone, cardiac output, and cerebrovascular-mediated mechanisms were considered by the authors to preserve cerebral oxygenation. To simplify, we classified the included heterogeneous studies based on whether the study authors used pharmacological (PPMs) or non-pharmacological prophylactic measures (NPPMs). For the prevention of MAP-dependent cerebral desaturations, PPMs were used in four RCTs (vasoactive agents; vasopressin [20,21,25], n = 3 and phenylephrine [7], n = 1) and NPPMs in eight (preloading with colloid [HES 130/0.4 [22], n = 1; SCD use on legs [26], n = 1; compression stockings [13,24], n = 2; targeted mild hypercarbia [27,28], n = 2; or reduced BCP angle for surgery [23] [low BCP angle, ≤ 60°, n = 1] or RIPC [29], n = 1]). However, overlapping prophylactic measures were observed among the study groups. Eight study groups [13,20,21,24] used compression stockings and five used SCDs [23,24,26] as a prophylactic measure. Crystalloid loading [7,21,22,29] and HES preloading [22,26,27] were used in 10 and 5

study groups, respectively. Vasoactive agent prophylaxis [7,20,21,25] was used in seven, whereas targeted mild hypercarbia [27,28] was used in two study groups. Similarly, low BCP angle [13,23,24] during surgery was used in five study groups. However, the RIPC technique was used in only a single study [29] group.

CDE was uniformly defined as > 20% decrease from baseline values and critical desaturation as < 55% (absolute value, Supplementary Material 3). Four studies [20,21,25,27] mentioned a duration of cerebral desaturation of > 15 s, whereas others had no duration stated. One study [29] additionally defined CDE as a fall in absolute values < 40% from baseline if it occurred for at least 1 min. Deliberate hypotension was accepted in one study [23]. All studies considered pharmacological agents for treating BCP-induced hypotension or treating CDEs *via* blood pressure elevation. The rest of the data related to treatment and prophylactic measures are depicted in Supplementary Material 3.

## Primary outcomes

*Absolute values of rSO₂ for an early period*

Pooled absolute $rSO_2$ (comparisons with controls, Figs. 1A and 1B) values (in %) were obtained for the first 15 min of BCP. These were recorded from 10 studies; three used vasopressin as a PPM [20,21,25] and seven used NPPM techniques [13,22,23,26–29] to prevent CDEs. PPMs were associated with lower absolute $rSO_2$ values than those without (controls). PPMs thus produced unfavorable results (vs. controls; MD: −13.58%, 95% CI [−16.03, −11.4], $I^2$ = 0%, P = 0.97) in contrast to NPPMs (vs. controls; MD: 2.76%, 95% CI [0.62, 4.89], $I^2$ = 56%, P = 0.03). Among NPPMs, the SCD and RIPC measures had statistically significantly higher $rSO_2$ values than in those without their use.

*Absolute values of rSO₂ for all-time period*

Pooled absolute $rSO_2$ (comparisons with controls, Figs. 2A and 2B) values (in %) were obtained for all-time periods of BCP. These were recorded from 10 studies, four of which used PPMs (vasopressin [20,21,25] or phenylephrine [7] infusions) to regulate MAP. Preloading with HES [22], reduction of BCP angle [23], SCDs [26], and RIPC [29] were used in one study each, and targeted mild hypercarbia [27,28] was used in two RCTs. PPMs were associated with lower absolute all-time overall $rSO_2$ values (vs. controls: MD, −12.23%; 95% CI, −14.59 to −9.87; $I^2$ = 0%, P = 0.82) in contrast to NPPMs (vs. controls: MD, 2.92%; 95% CI, 0.34 (vs. controls; MD: −12.23%, 95% CI [−14.59, −9.87], $I^2$ = 0%, P = 0.82) in contrast to NPPMs (vs. controls; MD: 2.92%, 95% CI [0.34, 5.49], $I^2$ = 76%, P = 0.0009). Among NPPMs, the use of SCDs, targeted mild hypercarbia, and RIPC measures had statisti-

cally significantly higher $rSO_2$ values than those without their use.

*Lowest achieved absolute rSO₂ values*

The lowest achieved $rSO_2$ (comparisons with controls, Figs. 3A and 3B) was recorded (in %) from nine studies. Three of these used PPMs (vasopressin [20,21,25] infusions), and NPPMs were used in others (preloading with HES [22], reduction of BCP angle [23], SCDs [26], and RIPC [29] techniques in one study each; targeted mild hypercarbia [27,28] in two). PPMs had lower $rSO_2$ for 'lowest achieved' absolute values during BCP compared to their controls (MD: −12.72%, 95% CI [−15.28, −10.15], $I^2$ = 0%, P = 0.99). However, the use of NPPMs was associated with higher values than in the control group patients for the same studied parameter (vs. controls; MD: 4.87%, 95% CI [2.69, 7.05], $I^2$ = 30%, P = 0.21). More specifically, use of targeted mild hypercarbia, SCDs, and RIPC techniques had favorable effects on $rSO_2$ compared to those without their use.

*Prophylactic measures and SjvO₂*

The $SjvO_2$ values (comparisons with controls, Figs. 1C, 2C, and 3C) were recorded for only the PPM subgroup in three studies [20,21,25] (150 patients). Arginine vasopressin (AVP) was used in all studies, and both $rSO_2$ and $SjvO_2$ were monitored. The early, all-time overall and lowest achieved $SjvO_2$ values were considered for analysis. With the use of prophylactic AVP infusions, the study group had comparable values to those of the control group patients, indicating the absence of beneficial effects of AVP in BCP. Furthermore, in contrast to $rSO_2$, the negative effects of AVP were not observed for the BCP $SjvO_2$ values.

*Meta-regression results for 'baseline to all-time overall rSO₂ differences'*

Meta-regression analysis included 11 studies [7,13,20–23,25–29]. One study [24] did not report baseline values; therefore, the study was not considered for meta-regression analysis. Meta-regressions revealed a statistically significant highest estimate (estimate: 7.8, SE: 1.534, 95% CI [4.8, 10.8], P < 0.001) for vasoactive agent prophylaxis use (PPMs, higher positive coefficients represent a greater fall of $rSO_2$ in BCP compared to supine) compared to NPPMs (Table 1A). The use of SCDs, crystalloid loading, targeted mild hypercarbia, HES, and RIPC had beneficial effects (visual analysis of coefficients, Table 1A). The use of compression stockings and maintenance of a low BCP angle during surgery failed to demonstrate these benefits.

In contrast, targeted mild hypercarbia, HES, and RIPC techniques had statistically significant coefficients (Omnibus P < 0.001, test for heterogeneity P = 0.646, Egger's P = 0.514, Table 2;
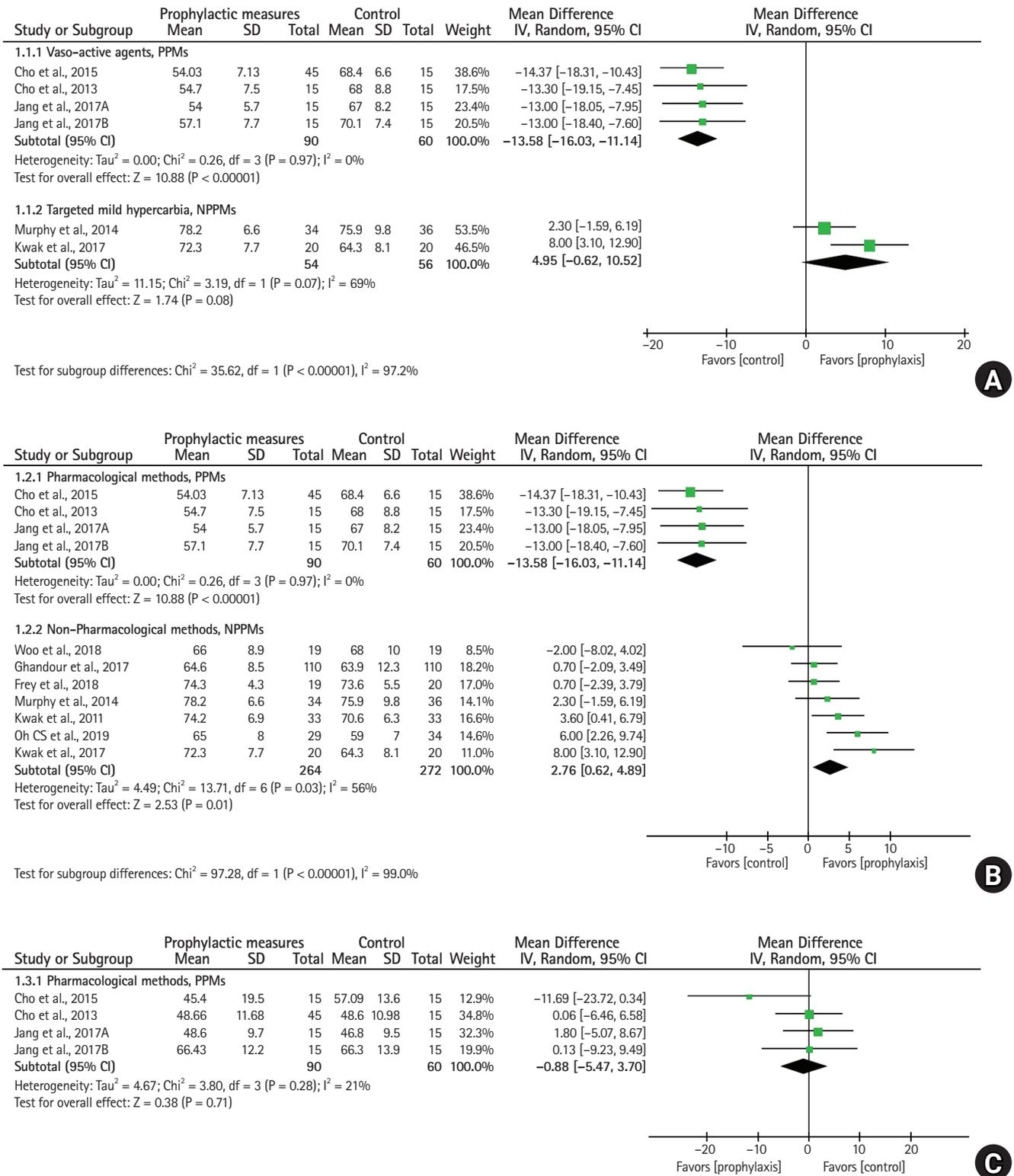
**Fig. 1.** Forest plots depicting (A) absolute values of $rSO_2$ for early period (first 15 min of BCP) for vasoactive agents and targeted mild hypercarbia techniques, (B) absolute values of $rSO_2$ for early period (first 15 min of BCP) based on whether prophylactic measures are pharmacological or non-pharmacological, and (C) absolute values of $SjvO_2$ for an early time period for PPMs. The mean differences between individual trials and 95% CIs are shown for prophylactic measures. Absolute values are expressed in %. The overall effects for each prophylactic measure and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. IV: inverse variance, NPPM: non-pharmacological prophylactic methods, PPM: pharmacological prophylactic methods, $rSO_2$: regional cerebral oxygen saturation, $SjvO_2$: jugular venous oxygen saturation.
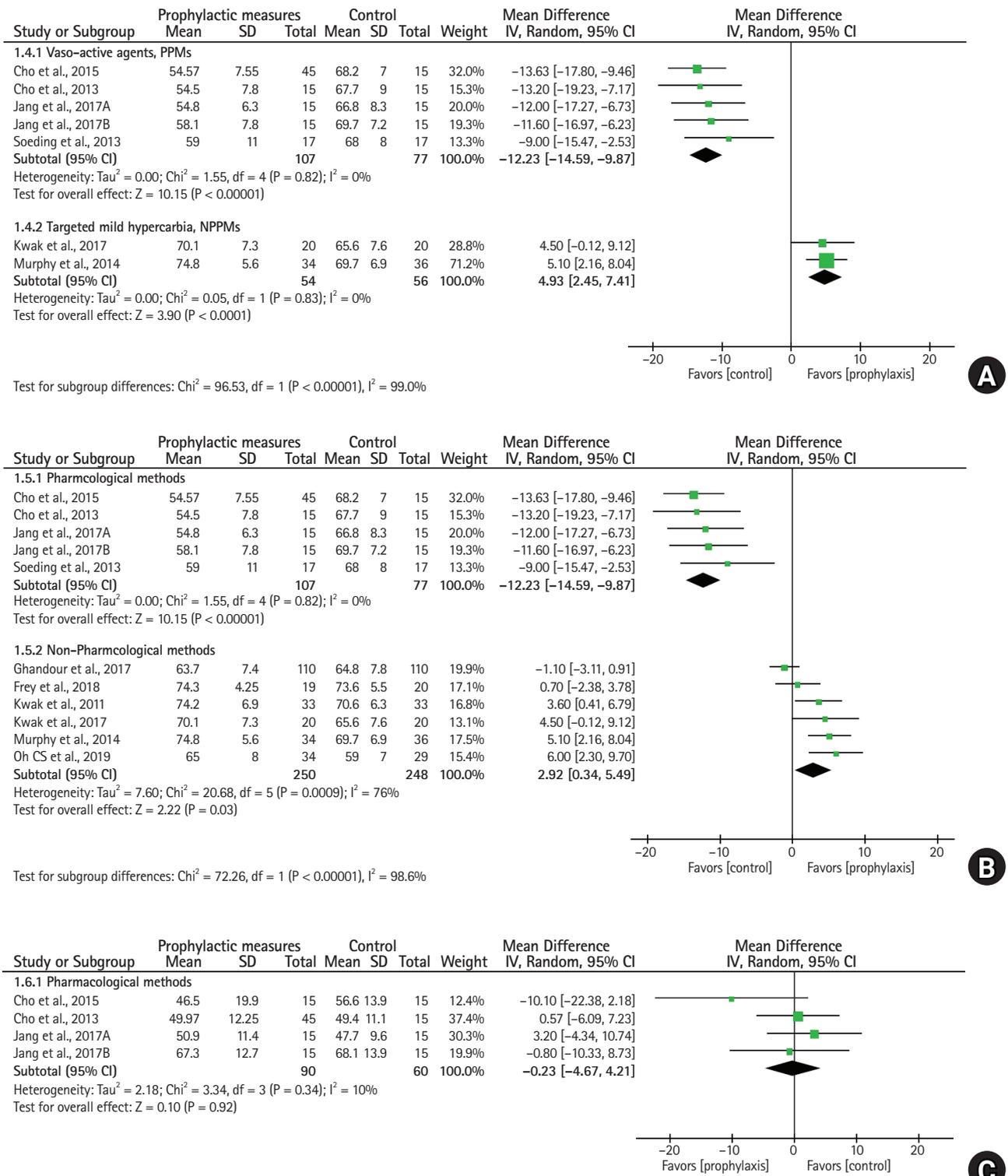
**Fig. 2.** Forest plots depicting (A) absolute values of $rSO_2$ for an all-time period for vasoactive agents and targeted mild hypercarbia techniques, (B) absolute values of $rSO_2$ for an all-time period based on whether prophylactic measures are pharmacological or non-pharmacological, and (C) absolute values of $SjvO_2$ for all-time period for PPMs. The mean differences between individual trials and 95% CIs are shown for prophylactic measures. Absolute values are expressed in %. The overall effects for each prophylactic measure and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. IV: inverse variance, NPPM: Non-Pharmacological Prophylactic Methods, PPM: Pharmacological Prophylactic Methods, $rSO_2$: regional cerebral oxygen saturation, $SjvO_2$: jugular venous oxygen saturation.
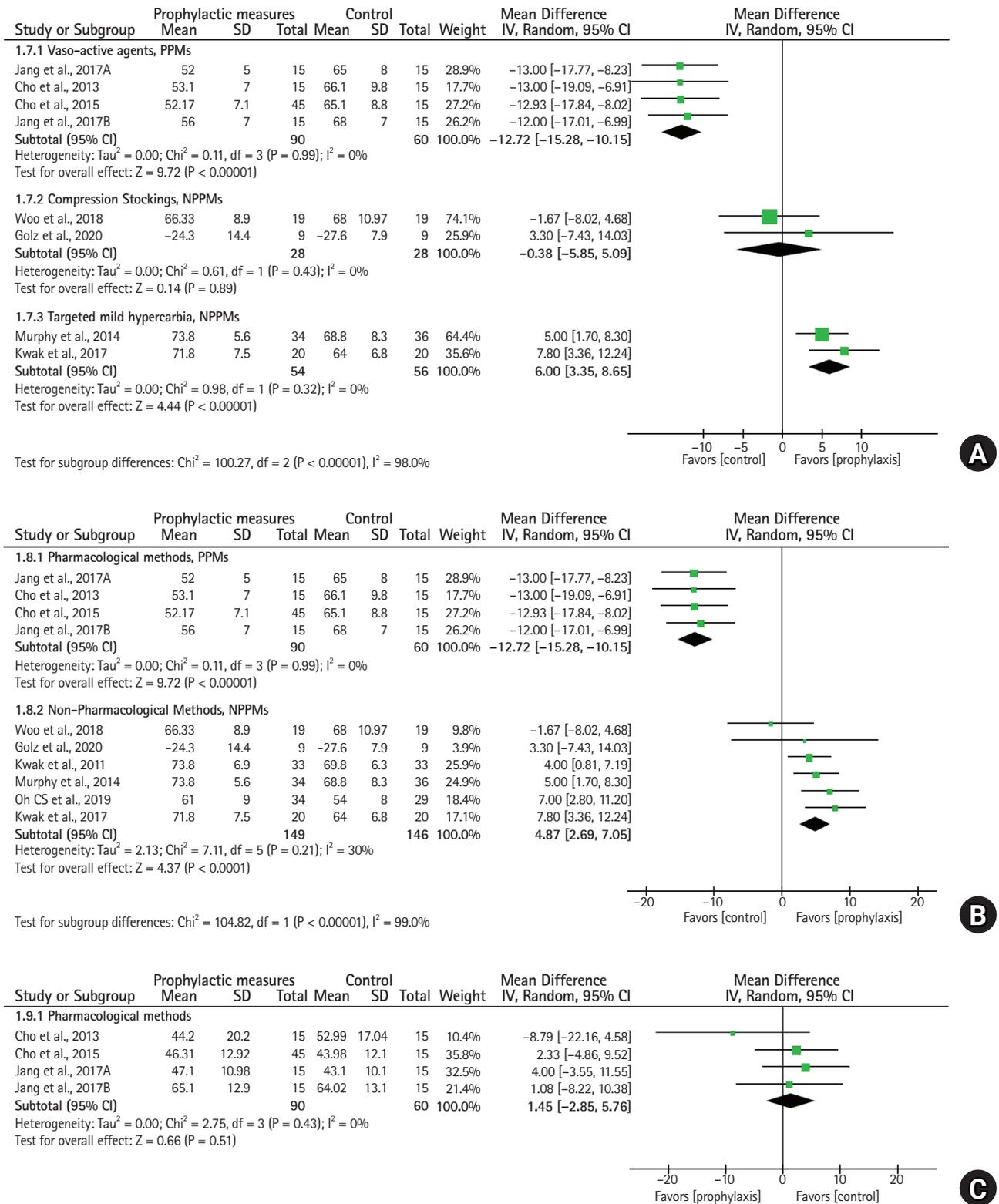
**Fig. 3.** Forest plots depicting (A) absolute values for lowest achieved $rSO_2$ for vasoactive agent, compression stockings, and targeted mild hypercarbia techniques, (B) subgroup analysis for lowest achieved $rSO_2$, based on whether prophylactic measures are pharmacological or non-pharmacological, and (C) $SjvO_2$ changes for lowest achieved values for PPMs. The mean differences between individual trials and 95% CIs are shown for prophylactic measures. Absolute values are expressed in %. The overall effects for each prophylactic measure and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. IV: inverse variance, NPPM: non-pharmacological prophylactic methods, PPM: pharmacological prophylactic methods, $rSO_2$: regional cerebral oxygen saturation, $SjvO_2$: jugular venous oxygen saturation.

**Table 1.** Meta-regression Analysis

| Prophylactic measure | Estimate (SE, 95% CI) | P value | Model fit |
|---|---|---|---|
| A. All-time overall rSO$_2$ | | | |
| Intercept | 7.8 (0.892, 6.1 to 9.6) | < 0.001 | Omnibus P < 0.001 |
| Compression stocking (Y) | 0.2 (1.491, –2.8 to 3.1) | 0.921 | Heterogeneity P = 0.646 |
| Sequential compression device (Y) | –1.6 (1.184, –3.95 to 0.7) | 0.167 | Egger's P = 0.514 |
| Low BCP angle (Y) | 1.2 (1.525, –1.8 to 4.2) | 0.438 | Log-likelihood, –37.9 |
| Regional ischemic preconditioning (Y) | –2.5 (1.018, –4.5 to –0.5) | 0.014 | Deviance, 75.8 |
| Crystalloid loading (Y) | –0.9 (0.99, –2.8 to 1.1) | 0.387 | AIC, 104.1 |
| Hydroxyethyl starch (Y) | –3.5 (1.043, –5.5 to –1.5) | < 0.001 | |
| Targeted mild hypercarbia (Y) | –5.5 (1.408, –8.2 to –2.7) | < 0.001 | |
| Vasoactive agents (Y) | 7.8 (1.534, 4.8 to 10.8) | < 0.001 | |
| B. Number of patients developing CDEs | | | |
| Intercept | 20.3 (6.487, 7.6 to 32.99) | 0.002 | Omnibus P = 0.459 |
| Compression stocking (Y) | 0.5 (6.335, –11.9 to 12.9) | 0.937 | Heterogeneity P < 0.01 |
| Sequential compression device (Y) | –10.2 (8.375, –26.6 to 6.3) | 0.225 | Egger's P = 0.299 |
| Low BCP angle (Y) | 3.025 (8.235, –13.1 to 19.2) | 0.713 | Log-likelihood, –50.2 |
| Regional ischemic preconditioning (Y) | –2.527 (12.641, –27.3 to 22.3) | 0.842 | Deviance, 100.3 |
| Crystalloid loading (Y) | –10.752 (6.848, –24.2 to 2.7) | 0.116 | AIC, 120.3 |
| Hydroxyethyl starch (Y) | –8.924 (8.193, –24.98 to 7.1) | 0.276 | |
| Targeted mild hypercarbia (Y) | –12.31 (10.14, –32.2 to 7.6) | 0.225 | |
| Vasoactive agents (Y) | 5.734 (7.632, –9.2 to 20.7) | 0.452 | |

Meta-regression analysis of prophylactic measures used across the study groups. (A) Pre-BCP (supine, after anesthesia induction) and BCP (all-time overall, absolute, and pooled) cerebral saturation values were considered for meta-regression depending on the use of prophylactic measures (yes vs. no). (B) Meta-regressions of 'number of patients experiencing CDEs', where baseline supine, pre-BCP CDEs were assumed as 'zero' for the analysis. All meta-regressions were performed using the restricted maximum likelihood method and random effects. AIC: Akaike information criterion, BCP: beach chair position, CDE: cerebral desaturation event, rSO$_2$: regional cerebral oxygen saturation, SE: standard error, Y: yes.

for publication bias [30], Supplementary Material 4A). Among all NPPMs, the targeted mild hypercarbia technique had the lowest estimates (estimate: –5.5, SE: 1.408, 95% CI [–8.2, –2.7], P < 0.001), indicating its superior beneficial effects over others (Wald test, P < 0.001).

## Secondary outcomes

### Number of patients developing CDEs

Ten studies reporting patients with CDEs [7,13,20–24,27–29] were included, and two [7,29] of these declared only patients with critical CDEs. Meta-analysis (Fig. 4A) revealed that use of PPMs showed a significantly higher risk of developing CDEs than that of the control groups (vs. controls; RR: 4.01, 95% CI [1.82, 8.81], I$^2$ = 0%, P = 0.75). In contrast, there was no difference observed between NPPMs and their respective controls (vs. controls; RR: 0.44, 95% CI [0.18, 1.10], I$^2$ = 75%, P = 0.001).

### Incidence of hypotension

Ten studies [7,13,20–22,25–29] reported episodes of hypoten-

sion. Both methods (PPMs and NPPMs) effectively reduced the incidence of hypotension (for PPMs vs. controls; OR: 0.13, 95% CI [0.06, 0.28], I$^2$ = 0%, P = 0.42, and for NPPMs vs. controls; OR: 0.27, 95% CI [0.10, 0.74], I$^2$ = 54%, P = 0.07) (Fig. 4B).

### Vasopressor consumption

Phenylephrine was used in five studies [20,21,23,24,29], and ephedrine in nine [13,20,21,24–29] (combined use in five studies [21,23,24,27,29]), as vasopressors for the treatment of BCP-induced hypotension. The diversity in pattern and dose of individual vasopressor use precluded any analysis of their effect on altering the CDEs.

A few studies compared cerebral desaturations with respect to time-person observations, such as time from induction or time from upright positioning to the onset of CDE, and average cumulative CDE durations. However, the data were inadequate for additional analyses. Serious adverse neurological outcomes (as reported by all studies) and postoperative cognitive dysfunction (as reported by three studies [20,21,25]) were not observed. One study [28] reported nausea and vomiting with low incidence in

**Table 2.** Summary of Results with GRADE of Evidence

| No. | Outcomes | Studies | Number of participants | Relative effect; MDs (%) or RR/OR (95% CI) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| 1 | Absolute values for $rSO_2$ for early period - PPMs | 3 | 150 | –13.58 (–16.03, –11.4) | ⊕⊕⊕◯, moderate |
| 2 | Absolute values for $SjvO_2$ for early period - PPMs | 3 | 150 | –0.88 (–5.47, 3.7) | ⊕⊕⊕◯, moderate |
| 3 | Absolute values for $rSO_2$ for all-time period - PPMs | 4 | 184 | –12.23 (–14.6, –9.87) | ⊕⊕⊕◯, moderate |
| 4 | Absolute values for $SjvO_2$ for all-time period - PPMs | 3 | 150 | –0.23 (–4.67, 4.21) | ⊕⊕⊕◯, moderate |
| 5 | Absolute values for lowest $rSO_2$ achieved - PPMs | 3 | 150 | –12.72 (–15.28, –10.15) | ⊕⊕⊕◯, moderate |
| 6 | Absolute values for lowest $SjvO_2$ achieved - PPMs | 3 | 150 | 1.45 (–2.85, 5.76) | ⊕⊕⊕◯, moderate |
| 7 | Number of patients developing CDEs - PPMs (event) | 3 | 124 | RR 4.01 (1.82, 8.81) | ⊕⊕◯◯, low |
| 8 | Number of patients developing hypotension episodes - PPMs | 4 | 184 | OR 0.13 (0.06, 0.28) | ⊕⊕◯◯, low |
| 9 | Number of patients developing hypotension episodes - NPPMs | 6 | 316 | OR 0.27 (0.10, 0.74) | ⊕⊕◯◯, low |
| 10 | Effect of targeted mild hypercarbia techniques (all-time overall for absolute $rSO_2$ values) | 2 | 110 | 4.93 (2.45, 7.41) | ⊕⊕⊕◯, moderate |
| 11 | Effect of targeted mild hypercarbia techniques (lowest achieved absolute $rSO_2$ values) | 2 | 110 | 6.0 (3.35, 8.65) | ⊕⊕⊕◯, moderate |
| 12 | Effect of targeted mild hypercarbia techniques (Pre-BCP to BCP fall in absolute $rSO_2$ values) | 2 | 108 | 1.56 (–0.71, 3.83) | ⊕⊕⊕◯, moderate |
| 13 | Effect of targeted mild hypercarbia techniques (number of patients developing fall in $rSO_2$, event) | 2 | 110 | RR 0.15 (0.05, 0.42) | ⊕⊕⊕◯, moderate |
| 14 | Effect of compression stockings (lowest achieved absolute $rSO_2$ values) | 2 | 56 | –0.38 (–5.85, 5.09) | ⊕⊕◯◯, low |
| 15 | Effect of compression stockings (number of patients developing CDEs, event) | 2 | 104 | RR 1.20 (0.75, 1.93) | ⊕⊕◯◯, low |

CDE: cerebral desaturation event, GRADE: Grading of Recommendations Assessment, Development and Evaluation, MD: mean difference, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological prophylactic methods, RR: risk ratio, $rSO_2$: regional oxygen saturation, $SjvO_2$: jugular venous oxygen saturation.
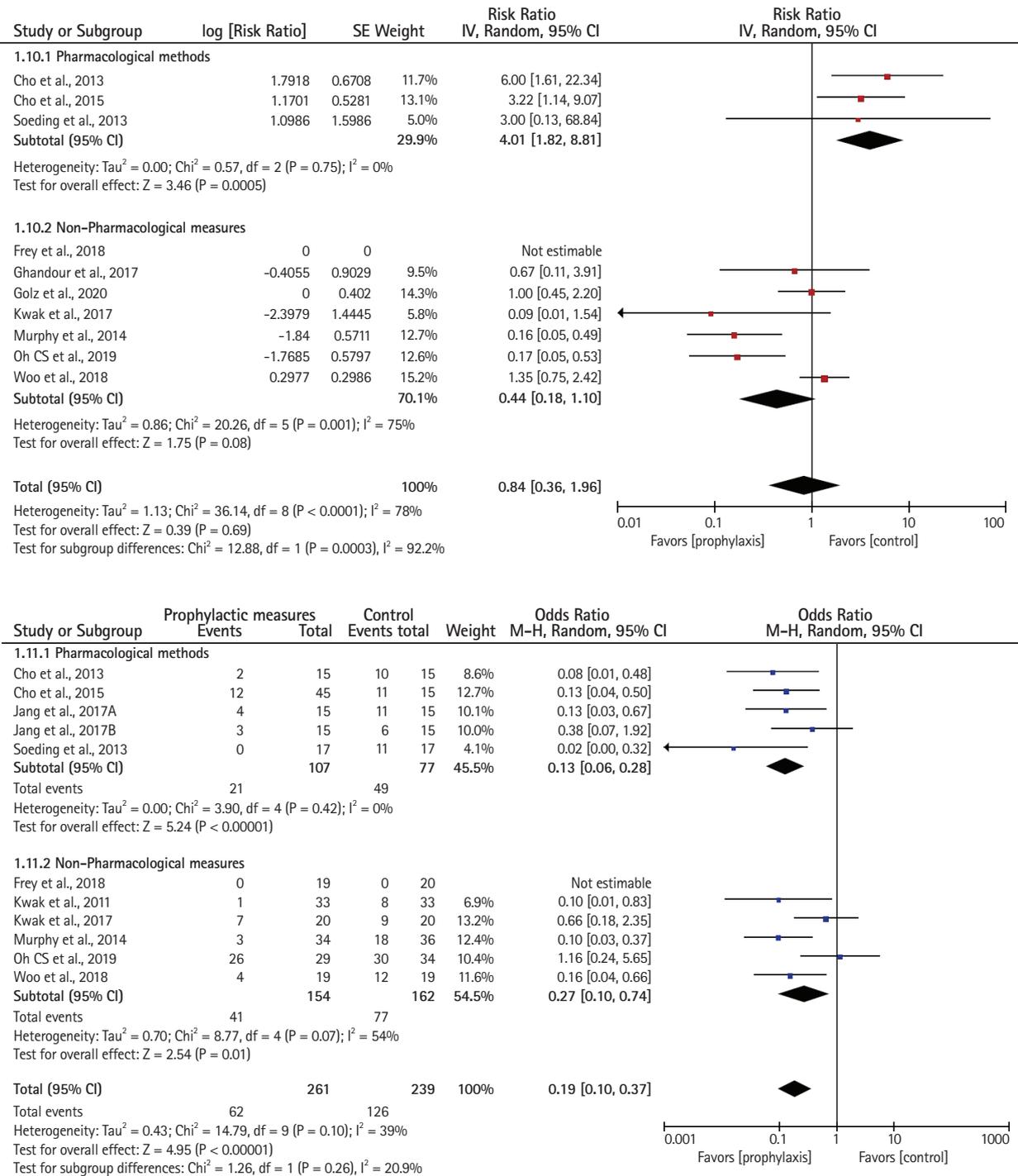
the study group (nausea/vomiting, 3/0 vs. 12/1, P < 0.05).

*Meta-regression results for 'number of patients experiencing CDEs'*

Meta-regression analysis of the number of patients experiencing CDEs (Table 1B) included 10 studies [7,13,20–24,27–29]. Two studies [25,26] did not report the incidence with respect to the number of patients; therefore, they were not considered in the meta-regression analysis. Meta-regressions revealed statistically significant highest estimate (estimate: 5.73, SE: 7.632, 95% CI [–9.2, 20.7], P = 0.452) for vasoactive agent prophylaxis use (PPMs, positive coefficient represents a higher number of patients experiencing CDEs) compared to that for NPPMs. Among all NPPMs, the targeted mild hypercarbia techniques had the lowest estimates observed, indicating its maximal effects over others (estimate: –12.31, SE: 10.14, 95% CI [–32.2, 7.6], P = 0.225). However, to statistically confirm the observations, poor model fit and high heterogeneity were limitations. We observed no statistically significant P values for any of the prophylactic measures used (Omnibus test for model coefficient P = 0.459; fit measure log-likelihood = –50.15, AIC = 120.3; Table 1B; for publication bias [30], see Supplementary Material 4B).

*Subgroup analysis of PPMs, targeted mild hypercarbia, and compression stockings*

Two studies [27,28] included 110 patients for the targeted mild hypercarbia techniques. End-tidal $CO_2$ values of 40–42 and 30-35 mmHg were used during BCP in the study and control patients, respectively. Subgroup analysis revealed targeted mild hypercarbia as an effective measure in preserving cerebral oxygenation ([vs. controls; MD: 4.93%, 95% CI [2.45, 7.41], $I^2$ = 0%, P = 0.83, Fig. 2A] and [vs. controls; MD: 6.00%, 95% CI [3.35, 8.65], $I^2$ = 0%, P = 0.32, Fig. 3A], for all-time overall and lowest achieved absolute $rSO_2$, respectively). Similar to the above results, targeted mild hypercarbia successfully prevented the fall of $rSO_2$ values from supine-baseline values to BCP (supine vs. BCP; MD: 1.56%, 95% CI [–0.71, 3.83], $I^2$ = 6%, P = 0.30, n = 108). This is in contrast to control patients without targeted mild hypercarbia use, in whom a significant fall of $rSO_2$ values from supine-baseline to BCP was observed (supine, pre-BCP vs. BCP; MD: 6.14%, 95% CI [3.08, 9.2], $I^2$ = 36%, P = 0.21, n = 112). Furthermore, the number of patients not developing CDE was 13 times higher than for those not using targeted mild hypercarbia techniques at BCP (OR, non-event: 13.18, 95% CI [3.84, 45.24], $I^2$ = 0%, P = 0.94, n = 110). Use of compression stockings [13,24] (n = 104) failed to demon-

| Study or Subgroup | log [Risk Ratio] | SE | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|
| **1.10.1 Pharmacological methods** | | | | | |
| Cho et al., 2013 | 1.7918 | 0.6708 | 11.7% | 6.00 [1.61, 22.34] | |
| Cho et al., 2015 | 1.1701 | 0.5281 | 13.1% | 3.22 [1.14, 9.07] | |
| Soeding et al., 2013 | 1.0986 | 1.5986 | 5.0% | 3.00 [0.13, 68.84] | |
| **Subtotal (95% CI)** | | | 29.9% | **4.01 [1.82, 8.81]** | |

Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)

| | | | | | |
|---|---|---|---|---|---|
| **1.10.2 Non-Pharmacological measures** | | | | | |
| Frey et al., 2018 | 0 | 0 | | Not estimable | |
| Ghandour et al., 2017 | -0.4055 | 0.9029 | 9.5% | 0.67 [0.11, 3.91] | |
| Golz et al., 2020 | 0 | 0.402 | 14.3% | 1.00 [0.45, 2.20] | |
| Kwak et al., 2017 | -2.3979 | 1.4445 | 5.8% | 0.09 [0.01, 1.54] | |
| Murphy et al., 2014 | -1.84 | 0.5711 | 12.7% | 0.16 [0.05, 0.49] | |
| Oh CS et al., 2019 | -1.7685 | 0.5797 | 12.6% | 0.17 [0.05, 0.53] | |
| Woo et al., 2018 | 0.2977 | 0.2986 | 15.2% | 1.35 [0.75, 2.42] | |
| **Subtotal (95% CI)** | | | 70.1% | **0.44 [0.18, 1.10]** | |

Heterogeneity: Tau² = 0.86; Chi² = 20.26, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 1.75 (P = 0.08)

| | | | | | |
|---|---|---|---|---|---|
| **Total (95% CI)** | | | 100% | **0.84 [0.36, 1.96]** | |

Heterogeneity: Tau² = 1.13; Chi² = 36.14, df = 8 (P < 0.0001); I² = 78%
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Chi² = 12.88, df = 1 (P = 0.0003), I² = 92.2%

0.01   0.1   1   10   100
Favors [prophylaxis]   Favors [control]

**(A)**

| Study or Subgroup | Prophylactic measures Events | Total | Control Events | total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.11.1 Pharmacological methods** | | | | | | | |
| Cho et al., 2013 | 2 | 15 | 10 | 15 | 8.6% | 0.08 [0.01, 0.48] | |
| Cho et al., 2015 | 12 | 45 | 11 | 15 | 12.7% | 0.13 [0.04, 0.50] | |
| Jang et al., 2017A | 4 | 15 | 11 | 15 | 10.1% | 0.13 [0.03, 0.67] | |
| Jang et al., 2017B | 3 | 15 | 6 | 15 | 10.0% | 0.38 [0.07, 1.92] | |
| Soeding et al., 2013 | 0 | 17 | 11 | 17 | 4.1% | 0.02 [0.00, 0.32] | |
| **Subtotal (95% CI)** | | 107 | | 77 | 45.5% | **0.13 [0.06, 0.28]** | |
| Total events | 21 | | 49 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 3.90, df = 4 (P = 0.42); I² = 0%
Test for overall effect: Z = 5.24 (P < 0.00001)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **1.11.2 Non-Pharmacological measures** | | | | | | | |
| Frey et al., 2018 | 0 | 19 | 0 | 20 | | Not estimable | |
| Kwak et al., 2011 | 1 | 33 | 8 | 33 | 6.9% | 0.10 [0.01, 0.83] | |
| Kwak et al., 2017 | 7 | 20 | 9 | 20 | 13.2% | 0.66 [0.18, 2.35] | |
| Murphy et al., 2014 | 3 | 34 | 18 | 36 | 12.4% | 0.10 [0.03, 0.37] | |
| Oh CS et al., 2019 | 26 | 29 | 30 | 34 | 10.4% | 1.16 [0.24, 5.65] | |
| Woo et al., 2018 | 4 | 19 | 12 | 19 | 11.6% | 0.16 [0.04, 0.66] | |
| **Subtotal (95% CI)** | | 154 | | 162 | 54.5% | **0.27 [0.10, 0.74]** | |
| Total events | 41 | | 77 | | | | |

Heterogeneity: Tau² = 0.70; Chi² = 8.77, df = 4 (P = 0.07); I² = 54%
Test for overall effect: Z = 2.54 (P = 0.01)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | 261 | | 239 | 100% | **0.19 [0.10, 0.37]** | |
| Total events | 62 | | 126 | | | | |

Heterogeneity: Tau² = 0.43; Chi² = 14.79, df = 9 (P = 0.10); I² = 39%
Test for overall effect: Z = 4.95 (P < 0.00001)
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.9%

0.001   0.1   1   10   1000
Favors [prophylaxis]   Favors [control]

**(B)**

**Fig. 4.** Forest plots depicting numbers of patients who developed (A) CDEs and (B) hypotension. The individual trials' RRs or ORs, SEs, and the pooled estimates are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. Natural log transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological prophylactic methods, RR: risk ratio, rSO$_2$: regional cerebral oxygen saturation, SE: standard error, SjvO$_2$: jugular venous oxygen saturation.

strate benefits, as the odds ratio remained less than 1 (OR, non-event: 0.77, 95% CI [0.33, 1.77], I² = 0%, P = 0.45). Furthermore, the lowest achieved rSO$_2$ was not different from that of control patients when compression stockings were used as a prophylactic measure (vs. controls; MD: −0.38%, 95% CI [−5.85, 5.09], I² = 0%, P = 0.43, n = 56).

*Risk of bias and heterogeneity*

The risk of bias summary and graph are presented in Figs. 5A and 5B, respectively. Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence was noted in one study [23], and selection bias due to inadequate concealment of allocations prior to the assignment occurred in a few studies [20,21,23]. Blinding is difficult [13,23,28] in BCP surgeries, although most studies were double-blinded. Therefore, performance bias and detection bias due to knowledge of the allocated interventions by participants and personnel during the study were observed in a few studies [13,28]. Further, we observed selective reporting (reporting bias) in a few [7,24], with incomplete outcome data such as reporting only 'critical' desaturations and mentioning 'maximum fall' of $rSO_2$ from baseline values. The observed low heterogeneity for PPMs precluded further analysis, as opposed to that of NPPMs. As described earlier, the latter group included the use of different prophylactic techniques. Therefore, the results of subgroup analyses of NPPMs are uncer-

tain because of the uneven covariate distribution among groups. Furthermore, an insufficient number of studies per group was observed. Therefore, all these factors necessitated additional meta-regression analysis. To explore the potential causes of heterogeneity that could influence primary outcome results, anesthetic factors such as the type of anesthesia and induction or maintenance agents were not considered separately, primarily due to inadequate data.

## GRADE evidence

The relevant summary results are presented in Table 2 with GRADE evidence. The certainty of the evidence is summarized as 'moderate' for the outcome of 'early, all-time overall, and lowest achieved $rSO_2/SjvO_2$ values' since the risk of bias was 'serious' in nature. The certainty of the evidence is similar for the targeted mild hypercarbia technique. For the rest of the studied outcomes, the certainty of the evidence is described as 'low' since 'inconsistency' and 'imprecision' were 'serious'.

## Discussion

In our meta-analysis, we evaluated the efficacy of different prophylactic measures employed to prevent cerebral desaturation during shoulder surgeries performed in BCP. We observed that not all prophylactic measures were successful, and the methods did differ in efficacy. Our current study provides concrete evidence that PPMs cannot effectively prevent cerebral desaturation. The benefits of a few NPPM techniques, such as targeted mild hypercarbia, for maintaining cerebral oxygenation during BCP are also evident. However, a few trials have confirmed the protective effects of HES preloading, and studies of SCDs or RIPC are scarce. Our meta-analysis unequivocally confirmed the negative effect of vasoactive agents on $rSO_2$ values (but not on $SjvO_2$), highlighting
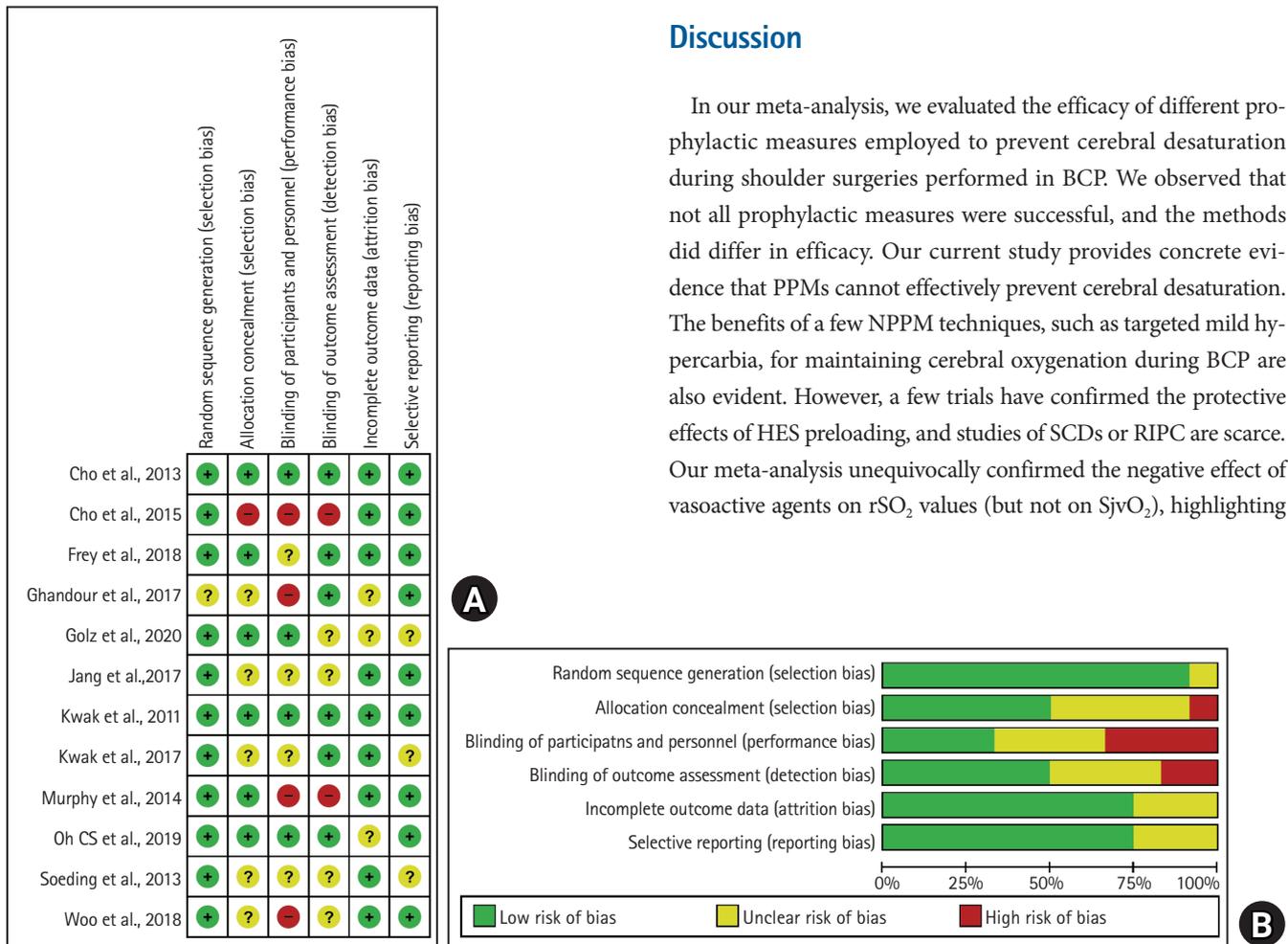


**Fig. 5.** Risk of bias summary (A) and graph (B).

their failure in protecting patients from CDEs despite their ability to prevent hypotension.

A pervasive issue in the pharmacologic prophylaxis portion of this meta-analysis is the extracranial contribution (contamination) [31] to cerebral oximetry, which must be acknowledged. This can be explained to a large extent as a 'paradoxical effect' of vasopressors on oximetry values when given to support blood pressure. Our analysis demonstrated that prophylactic vasoactive agents can decrease $rSO_2$ values. However, to confirm whether this decrease truly reflects cerebral desaturation, additional analysis was needed. $SjvO_2$-metry is a more accurate assessment of the balance between oxygen supply and demand in the brain, albeit globally. Therefore, we simultaneously analyzed the effects of PPM on both $rSO_2$ and $SjvO_2$. The discrepancy between $rSO_2$ and $SjvO_2$ necessarily describes the effects of PPMs on regional oximetry values. The other finding of this study is the inefficacy of vasoactive agent prophylaxis in preventing fall of cerebral oxygen saturation. Despite the higher $SjvO_2$ recorded over $rSO_2$, AVP failed to demonstrate any beneficial effect, in that its use did not prevent the fall in $SjvO_2$ during BCP. In contrast to $rSO_2$, the $SjvO_2$ values of the PPM subgroup were similar to those of the control groups, in both the supine, pre-BCP and BCP periods. A single phenylephrine study was included in the PPM subgroup. However, in the absence of $SjvO_2$ monitoring in the same study, we were unable to describe the extracranial effects of phenylephrine on $rSO_2$ monitoring. The association of AVP, CDEs, and postoperative cognitive dysfunction have also been reported in the past [32]. While some NPPMs were superior to vasoactive agent prophylaxis with respect to CDE incidence, their role in preventing cognitive dysfunction was not evaluated in our study. Reports on the effect of AVP on cerebral oxygenation in animal models have been conflicting [12,33]. Beyond auto-regulation values of MAP, AVP improves CBF via nitric oxide-mediated cerebral vasodilation [34], and this was the rationale for its use in some of our included studies.

In this review, the effectiveness of individual prophylactic measures (especially NPPMs) was analyzed through a separate analysis. Drawing conclusions on NPPMs was not possible, as we have lumped together with a disparate and diverse group. Importantly, since no study authors used a single measure to prevent cerebral desaturation, analyzing a single method (such as NPPMs) could be misleading. Therefore, the more appropriate method of meta-regression analysis was performed. Our analysis confirmed the beneficial effects of a few NPPMs, such as targeted mild hypercarbia, HES, and RIPC. Targeted mild hypercarbia during these procedures must be performed with caution and must not be performed to the exclusion of blood pressure support. Hypercarbia

impairs cerebral autoregulation and puts the patient at a higher risk for cerebral hypoperfusion, should hypotension occur at the same time. Additional subgroup analysis established stronger evidence for targeted mild hypercarbia use. Few prospective studies [35] investigating the effects of targeted mild hypercarbia on $rSO_2$ during major surgery have confirmed similar effects.

One of the interpretations of this meta-analysis is that NPPMs in combination can be effectively deployed during BCP surgery to enhance $rSO_2$; this conclusion could be relevant to clinicians in maintaining cerebral oxygenation. For example, targeted mild hypercarbia of 40–42 mmHg during controlled ventilation, appropriate preloading (HES), and concomitant use of SCDs can significantly reduce CDEs. The routine use of RIPC as a prophylactic measure has not yet been recommended. While a previous prospective cohort study [9] demonstrated the efficacy of compression stockings in reducing the incidence of CDEs, our meta-regression results failed to confirm this. Confounding factors such as MAP, hemoglobin level, cardiac output, angle of BCP maintained, and partial pressures of oxygen and carbon dioxide, which can influence $rSO_2$ values, were kept constant in the RCTs included. We believe that the study authors excluded patients with cardiopulmonary disease or anemia because of possible negative effects on $rSO_2$ values.

While PPMs were inferior to a few NPPMs in the prevention of CDEs (coefficient evaluation), both exhibited similar effects with respect to lowering the incidence of hypotension (vs. controls). Thus, PPMs were unable to achieve the ultimate therapeutic benefit, despite maintaining MAP. The association of episodic decrease in MAP with the incidence of cerebral desaturation and its direct correlation with cerebral oximetry values remain unconfirmed [36,37]. Several studies have demonstrated no direct correlation between blood pressure and cerebral (de)saturation values (Supplementary Material 5) [13,38–43]. However, cardiac output has been claimed as a factor that correlates well with $rSO_2$ values in BCP-neurosurgical patients [40]. Targeting MAP alone may not be the ideal approach to prevent CDEs in BCP surgeries.

Over 80% of the patients in this meta-analysis were treated with ephedrine for BCP-related hypotension. Phenylephrine and ephedrine are commonly used for this indication. While treating hypotension in a non-BCP setting, the former was shown to decrease cerebral oxygen saturation even with correction of arterial blood pressure [44]. According to cardiac output rather than arterial blood pressure, it has been concluded that treating hypotension using vasoconstrictors to avoid cerebral hypoxia actually accomplished the opposite result [44,45]. In contemporary practice, approximately 70% of BCP-related hypotension episodes are still treated with phenylephrine. It would be prudent to choose a dif-

ferent vasopressor and to use the more physiological NPPMs. Additionally, while targeting cardiac output to maintain cerebral oxygenation, the use of NPPMs with ephedrine (as a vasopressor of choice to treat hypotension) could possibly be a desirable combination. Currently, the use of cerebral oximetry in patients with BCP is limited in availability. Under these circumstances, especially in susceptible patients, this combination is gaining significance.

Our study had some limitations. Higher heterogeneity values represent different NPPM methods applied over cohorts. The type of anesthesia, maintenance anesthetics, Fraction of inspired oxygen concentration, and other co-variables could have partially influenced the outcomes. The definition of 'event' could vary according to the authors' perception, and this could have a bearing on the incidence reporting. The range of $rSO_2$ values may be significantly larger when measured with INVOS™ devices compared to FORE-SIGHT™, but the exact underlying reasons for these differences remain unknown [46]. The use of phenylephrine to treat hypotension episodes in subgroups of NPPMs could have possibly influenced the CDEs in a few studies, which is an inherent contradiction in the analysis. The difference in the timing of the application of NPPMs poses significant analytical challenges. Moreover, none of the included NPPMs reported $SjvO_2$ data. The use of pooled data and presuming the baseline data of $rSO_2$ values to be uniform for all patients may be another limitation. Non-availability of raw patient data and non-reporting of time-person observations for groups or lowest achieved cerebral desaturation data for many trials precluded conducting individual patient meta-analysis or correlations.

In conclusion, the evidence favors the prophylactic use of targeted mild hypercarbia techniques to effectively reduce BCP-CDEs and best preserve cerebral oxygenation. Evidence does not favor the use of prophylactic vasoactive agents for the prevention of cerebral desaturations, irrespective of whether their use interferes with cerebral oximetry readings. One may use a combination of a few NPPMs as prophylactic measures; however, an RCT investigating the effect of combined use of all NPPMs could conclusively demonstrate the benefits. At the same time, comparisons of prophylactic as well as therapeutic effects of different vasoactive agents (such as phenylephrine vs. ephedrine) for BCP-CDEs could set the direction for future research in this field.

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## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

## Author Contributions

Thrivikrama Padur Tantry (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Writing – original draft; Writing – review & editing)
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## Supplementary Materials

Supplementary Material 1. The search strategy. The search terms were used to search MEDLINE, CCRCT (Cochrane Central Register of Controlled Trials), CINHAL (Cumulative Index to Nursing and Allied Health Literature, EBSCO host), and Google Scholar (modified to suit each specific database with abstract, keywords, and text with the removal of duplicates).
Supplementary Material 2. The flow chart for literature identification and study selection. BCP: beach chair position, CDE: cerebral desaturation event, CCRCT: Cochrane Central Register of Controlled Trials, CINHAL: Cumulative Index to Nursing and Allied Health Literature, n: number of studies, $rSO_2$: regional cerebral oxygen saturation.
Supplementary Material 3. The study characteristics. ASA PS: American Society of Anesthesiologists physical status, AVP: arginine vasopressin, BCP: beach chair position, BL: baseline, BP: blood pressure, CBF: cerebral blood flow, CDE: cerebral desatura-

tion event, CS: compression stockings, DM: diabetes mellitus, Eph: ephedrine, GA: general anesthesia, HES: hydroxyethyl starch, HR: heart rate, HTN: hypertension, ICB: infraclavicular block, ISB: interscalene block, MAP: mean arterial pressure, MBP: mean blood pressure, $N_2O$: nitrous oxide, NA: not applicable, NE: norepinephrine, NP: not provided, $O_2$: oxygen, Phe: phenylephrine, $rSO_2$: regional saturation of oxygen in the brain, SCD: sequential compression device, TIVA: total intravenous anesthesia. Supplementary Material 4. Publication bias. The funnel plots for (A) pre-BCP (supine, after anesthesia induction) and BCP (all-time overall, absolute, and pooled) cerebral saturation values, (B) the number of patients experiencing the CDEs during meta-regressions of prophylactic factors to prevent cerebral desaturation. The regression test for funnel plot asymmetry (Egger's test) P values were > 0.05; however, poor model fit – fit measures were recorded for funnel plot B.

Supplementary Material 5. Studies depicting associations between MAP and $rSO_2$. Correlation analysis was used in most of the studies to establish the associations. BCP: beach chair position, BL: baseline, CDE: cerebral desaturation event, CO: cardiac output, DBP: diastolic blood pressure, $ETCO_2$: end-tidal carbon dioxide, eTMAP: estimated temporal mean arterial pressure, L: left-sided measurement, MAP: mean arterial pressure, MBP: mean blood pressure, NIBP: noninvasive blood pressure, NIRS: near-infrared reflectance spectrometry, R: right-sided measurement, r: correlation coefficient, $rSO_2$: regional cerebral oxygen saturation, SBP: systolic blood pressure, *INVOS™ (Somanetics, Troy, MI, USA) and **FORE-SIGHT™ (Cas Medical Systems Inc., Branfort, CT, USA), the names of cerebral oximeter equipments that measured the regional cerebral oxygen saturation.

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