Meta-Analysis

Adverse heart rate responses during beach-chair position for shoulder surgeries - A systematic review and meta-analysis of their incidence, interpretations and associations

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ABSTRACT

Background and Aims: Evaluations of adverse heart rate (HR)-responses and HR-variations during anaesthesia in beach-chair-position (BCP) for shoulder surgeries have not been done earlier. We analysed the incidence, associations, and interpretations of adverse HR-responses in this clinical setting. Methods: We performed a meta-analysis of trials that reported HR-related data in anaesthetised subjects undergoing elective shoulder surgeries in BCP. Studies included prospective, randomised, quasi-randomised and non-randomised, controlled clinical trials as well as observational cohorts. Literature search was conducted in MEDLINE, EMBASE, CINHAL and the Cochrane Central Register of Controlled Trials of the 21st century. In the first analysis, we studied the incidence and associations of bradycardia/hypotension-bradycardia episodes (HBE) with respect to the type of anaesthesia and different pharmacological agents. In the second, we evaluated anaesthetic influences, associations and inter-relationships between monitored parameters with respect to HR-behaviours. Results: Among the trials designed with bradycardia/HBE as a primary end point, the observed incidence of bradycardia was 9.1% and that of HBE, 14.9% and 22.7% [(for Interscalene block (ISB) ± sedation) subjects and general anaesthesia (GA) + ISB, respectively]. There was evidence of higher observed risk of developing adverse HR-responses for GA subjects over ISB (Risk Difference, \( P < 0.05 \)). Concomitant use of \( \beta \)-agonists did not increase risk of HBEs (\( P = 0.29, \, F = 11.4% \) ) or with fentanyl (\( P = 0.45, \, F = 0% \) ) for ISB subjects (subgroup analysis). Fentanyl significantly influenced the HR-drop over time (meta-regression, estimates (standard error), 14.9 (5.4), 9.8 (4.3) and 17 (2.6); \( P = 0.007, \, 0.024 \) and <0.001; for early, mid and delayed periods, respectively) in GA subjects. With respect to number of subjects experiencing cerebral desaturation events (CDEs), total intravenous anaesthesia (TIVA)-propofol had higher risk over inhalational anaesthesia (\( P = 0.006, \, F = 86.7% \) ). Meta-correlation analysis showed relationships between the HR and \( rSO_2 \) (regional cerebral oxygen saturation) or \( SjvO_2 \) (jugular venous oxygen saturation) values (\( r = 0.608, \, 95\% CI, 0.439 \) to 0.735, \( P < 0.001, \, F = 77.4% \) and \( r = 0.397, \, 95\% CI, 0.151 \) to 0.597, \( P < 0.001, \, F = 64.3% \), respectively). Conclusions: There is not enough evidence

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INTRODUCTION

Among the undesirable haemodynamic consequences of beach-chair position (BCP) for shoulder (arthroscopic) surgeries, bradycardia, by virtue of its unpredictable occurrence and occasionally adverse anaesthetic consequences, is a cause for concern. A specifically named haemodynamic event, the ‘Hypotension-Bradycardia Episode’ (HBE) has been reported in 6-27% of BCP subjects. These studies however lack specificity in documenting isolated significant bradycardia (necessitating the use of atropine). The true incidence of bradycardia remains indeterminate due to several factors such as the frequent use of the terms ‘bradycardia’ and ‘HBEs’ as synonyms, use of different definitions of ‘bradycardia’ by various authors, inclusion of additional causes of ‘hypotension’ episodes (anaesthetic and pharmacological) and subjective variations in the anaesthesiologist’s decision to use atropine, justifiably attributable to a ‘play it safe’ attitude.

The correlation of incidence of bradycardia/HBE with the type of anaesthesia or the anaesthetic agent deployed has not been conclusively established. While activation of the Bezold-Jarish Reflex (BJR) linked to interscalene block of the brachial plexus (ISB) could be the primary reason for such adverse events, the demonstration of a ‘non-empty’ heart ventricle during such events suggests otherwise. Similarly, the association of use of β-adrenergic agonists and adverse heart rate (HR)-responses/HBE is uncertain since these episodes were also reported in patients without their use. Likewise, while ISB has been linked to such events, the same has not been confirmed with general anaesthesia (GA). There is a paucity of comparative literature on the association of HR-responses in BCP with other parameters like use of maintenance anaesthetic agents or opioids. Several studies indicate a strong association of hypotensive response with regional cerebral oxygen saturation (rsO₂) and jugular venous oxygen saturation (SjvO₂) for BCP surgeries done under anaesthesia. But it is unclear whether cerebral desaturation events (CDEs) correlate with (adverse) HR-responses.

The aim of this study was to systematically review all available evidence from trials reporting bradycardia/HBEs for its: 1) incidence, 2) anaesthetic/pharmacological associations, and 3) association of BCP-HR-behaviours with monitored parameters, and to conduct a meta-analysis on the results. Establishing the association of adverse haemodynamic responses with specific anaesthesia-related variables or changes in monitored parameters would be helpful in improving predictability of such events, taking precautionary measures to prevent them and providing an insight into their possible underlying pathophysiological mechanisms.

METHODS

Registration and protocol

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-analyses. The protocol was registered with PROSPERO (CRD42019119454, crd.york.ac.uk; date of registration, 14/01/2019, and updated on 31/07/2019).

Eligibility criteria

We included prospective, randomised, quasi-randomised and non-randomised, controlled clinical trials as well as observational cohorts with adult subjects (>18 yrs) undergoing elective shoulder surgeries in BCP. Reporting of HR-related data or HR-responses were mandatory to inclusion. Publications in all languages were considered. Subjects received one of the following anaesthetic modalities: (1) Planned GA; (2) Regional anaesthesia (RA): ISB or similar and (3) RA in combination with GA. The use of supplementary sedation was not a barrier to inclusion. We excluded studies wherein subjects underwent...
surgeries in <45° BCP as well as American Society of Anaesthesiologists (ASA) >3 physical status.

**Information sources**

An electronic literature search was conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINHAL. The selection of literature specifically restricted to studies in BCP. We also searched the bibliography of retrieved manuscripts for additional studies pertaining to data encompassing our primary outcome of interest. These comprised studies reporting incidents of isolated bradycardia or HBEs, documenting maximum and minimum average HRs, or measuring serial HR over time periods; with a caveat that both pre-induction and post-induction HR data be available. Twenty-first-century literature were scanned since anaesthesia protocols have remained uniform during this period. Retrospective studies, reviews with inadequate information on primary outcome interests, abstracts and letters to the editor were not included. The detailed search strategy is shown in Supplementary Digital Content File 1.

**Study selection and data collection**

The manuscripts meeting the inclusion criteria were assessed and data were extracted following a standardised format. Extracted items comprised of study characteristics, risk of bias (RoB) domains,[18] participant disposition, and study outcomes. Patients were categorised according to type of the surgery or anaesthesia, number of subjects and position adopted for surgery (≥45° of BCP, i.e., 45 to 90°). Interventions referred to BCP after induction and achievement of hemodynamic stability. Comparison of variables was pre-BCP versus post-BCP. Outcomes were classified as ‘primary’ and ‘secondary’. The former included HR data before and after BCP at various intervals of time, the incidence of bradycardia/HBE in BCP, influence of anaesthetics over HR-responses and HR-rSO$_2$/SjvO$_2$ associations. The latter included incidence and magnitude of hypotension and associations of mean blood pressure (MBP) with anaesthetic factors, vasoactive drugs and rSO$_2$/SjvO$_2$ in BCP.

**Data synthesis and analysis of outcomes**

For evaluation of the outcome of interests of this interventional (investigating an effect of BCP on HR) meta-analysis, data were extracted separately from study groups (SGs) of each trial to negate the effect of intergroup variables affecting their outcomes. We categorised the SGs further into study control groups, randomised SGs, non-randomised SGs, physiological control groups. Study control groups received standard anaesthesia care without additional investigating pharmacological agents or technical measures. Physiological control groups were those placed in BCP but not anaesthetised.

The HR data collected included values documented at a single point of time or continuous data at various intervals for a SG. Incidences of bradycardia and/or HBE and rest of the HR data were considered for meta-analysis. Data were collected as a single or combined value in the form of mean and standard deviations (SD) or median and inter-quartile range (IQR), respectively. If multiple data were provided, then they were converted into pooled statistical averages. The data were tabulated under pre-induction [baseline (BL)] and post-induction groups. The latter included data relating to pre-BCP and post-BCP categories after the stabilisation of vitals. These post-BCP HR data were pooled for the time periods mentioned in the respective publication. If recorded data timings were non-specific timings, they were approximated to a specific time by mutual discussion with the two authors. Publications with unreported or inconclusive data that could not be obtained after attempts to contact the authors were excluded from this review.

The data presented in tables, text or images were used as the primary source for extraction. A graph digitizing software (Engauge Digitizer version 10.10, @ Mark Mitchell) was used for efficiently extracting and estimation of numerical raw data whenever text numerical data were unavailable. We substituted the missing SDs with pooled SDs of other studies with the same comparison by $V[(\sum N*SD)/\sum N]$ where N = sample size. When range and IQR were available, SD was estimated using the formula $SD = range/4$ and $SD = IQR/1.35$, respectively, as described by Cochrane Hand Book of Systematic Reviews.[19] Data were reported as 95% confidence intervals (CI). The median was used to estimate the mean if the value was not reported. Whenever standard error of mean (SEM) was reported, SD was obtained as $SD = SEM/\sqrt{N}$. If data were provided as % of change over a BL numerical value, they were converted to numbers. To account for drop out cases over time or termination of BCP before the time specified in the meta-analysis, subject 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.
We used individual definitions for defining events of bradycardia, HBE, hypotension and CDEs as described by authors of each study. Dichotomous data like bradycardia, hypotension, CDEs, etc. were converted into incidence \((n/N)\) for a given time interval. The single highest incidence was used to capture the proportion of subjects who experienced a certain adverse response at least once. Data from SGs receiving more than one intervention or different anaesthetic agent or a technique (within a SG) were combined into a single group as per Cochrane Handbook.\(^{[19]}\) Data were clubbed together into a single group whenever the primary authors grouped the study subjects on the basis of an event. Finally, ‘intention to treat’ basis was used for analysing complications-related data in some SGs. Subjects were repositioned back to supine following BCP-induced haemodynamic disturbances.\(^{[20]}\)

**Data synthesis specific to HR**

Incidence of bradycardia/HBE was considered whenever the events were reported either individually or synonymously in the subject at least once. To differentiate isolated bradycardia from the broader term, HBE, we considered the use of atropine \((n/N)\) for defining the former. Data relating to HR-variability over time were again sub-divided into immediate/early (~10 minutes, EHR), mid (11-30 minutes, MHR) and delayed (after 30 minutes till the end of BCP, DHR). The magnitude of changes over time was represented by mean differences (MDs).

**Data synthesis specific to blood pressures (BPs)**

MBP was considered for data evaluation and the data synthesis was similar to that followed for HR. We excluded pooled data of systolic or diastolic blood pressures. Whenever SDs were not reported for nadir values, they were imputed from pooled SDs of the same group. All analysis was done presuming no incidences of CDEs in supine position under anaesthesia. The single highest incidence was used to capture the proportion of subjects who experienced a certain adverse response at least once. Data from SGs receiving more than one intervention or different anaesthetic agent or a technique (within a SG) were combined into a single group as per Cochrane Handbook.\(^{[19]}\) Data were clubbed together into a single group whenever the primary authors grouped the study subjects on the basis of an event. Finally, ‘intention to treat’ basis was used for analysing complications-related data in some SGs. Subjects were repositioned back to supine following BCP-induced haemodynamic disturbances.\(^{[20]}\)

**Data synthesis specific to CDEs**

For analysing CDEs, two types of \(\text{rSO}_2\) values (MDs) were considered; (1) MDs of pre and post-BCP (pooled), as ‘absolute’ values; (2) MDs of pre-BCP and ‘lowest’ achieved post-BCP \(\text{rSO}_2\) values. Lowermost of lowest was considered whenever right and left cerebral hemispheres were recorded separately (with single or two different methods). Whenever SDs were not reported for nadir \(\text{rSO}_2\) values, they were imputed from pooled SDs of the same group. All analysis was done presuming no incidences of CDEs in supine position under anaesthesia.

**Pre-defined sources of heterogeneity**

To explore the potential causes of heterogeneity in our results that could influence primary outcome results, we pre-identified certain clinical aspects of individual SGs. These included (1) randomisation technique; (2) anaesthetic technique; (3) induction agent; (4) maintenance anaesthetic agent; (5) use of opioids; (6) use of vasoactive agents. Equivalent doses of ephedrine and phenylephrine were considered for vasopressor consumption, converting ephedrine doses to their phenylephrine equivalence using a potency ratio of 81.2: 1.\(^{[21]}\)

The degree to which some of these additional factors predict EHRs, MHRs and DHRs was evaluated using a meta-regression analysis. To examine the influence of different anaesthetic agents, opioids, vasoactive drugs or eligibility criteria on HR-variability, we performed a sensitivity analysis. Sub-group analysis was considered based on: (1) type of anaesthesia; (2) predisposing or preventing agent; or (3) the maintenance agent for both incidences of bradycardia/HBE and serial HR measurements. Additional analyses (‘leave-one-out’ analysis, correlation statistics and meta-correlation analysis) were considered as necessary (for primary outcomes).

Meta-analysis was conducted with Review Manager (RevMan) 5.3 (Cochrane Collaboration, Copenhagen, Denmark, 2014). The random effects model was used for all analyses. Heterogeneity was measured and expressed as \(I^2.\)^\(^{[22]}\) Meta-regression was performed using JASP software (Version 0.9.2, BibTeX, Amsterdam).\(^{[23]}\) This analysis excluded subjects administered with ISB ± sedation since the anaesthetic agent influences on HR are largely absent. Meta-regression (Restricted-Maximum-Likelihood method, random effects) was performed for EHR with priori defined factors, induction agents, opioids and use of PVIs. For MHR and DHR, maintenance anaesthetic agents and opioids were considered.

For continuous variables (HR, absolute and lowest achieved cerebral saturations), MDs were compared using the inverse-variance (I-V) method. For dichotomous variables (incidences of bradycardia, HBEs, CDEs, hypotension), odds ratio (OR), risk
ratio (RR) or risk differences (RD) were computed by the Mantel-Haenszel (M-H) or I-V methods. Natural log-transformation was adopted[24] as the outcomes for incidences were expected to be non-normal. Publication bias was checked using regression test for funnel plot asymmetry and Egger’s test [JASP software, version 0.9.2].[25] Correlations were attempted for those SGs which mentioned statistical averages of consecutive measurements of HR, rSO₂ and SjvO₂ on the one hand and for MBP and rSO₂ on the other. Meta-correlation analysis was performed after obtaining a series of correlation coefficients for various SGs using MedCalc® Version 14.8.1, MedCalc Software bvba, 2014. For all, statistical significance was set at $P < 0.05$ (2-tailed).

**RESULTS**

Summary of results for various outcomes are provided in Table 1.

**Literature identification**

From 2306 studies that were initially screened, 661 potentially relevant manuscripts were selected based on the abstract. The details pertaining to literature identification are provided in the flow chart (Supplementary Digital Content File 2). Finally, 47 trials provided the data for analysis (from year 2000 to 2019).

**Study characteristics**

We included all SGs of manuscripts that provided HR data. Hence, the majority of manuscripts had two or more SGs. Supplementary Digital Content File 3 summarises the characteristics of SGs including Jadad scores. In total, there were 91 SGs for this review ($n = 3107$), 70 SGs detailed about serial HR measurements, additional to the adverse HR-responses. There were 67 randomised SGs (RCTs, $n = 29$). Supplementary Digital Content File 4 depicts the RoB graph and summary. Thirty-nine SGs were considered as study control groups and four as physiological study controls. One trial (year 1998)[30] was included against the PRISMA protocol, as the same was used by the rest of the authors to define HBE.

**First analysis**

**Bradyardia and/or HBE**

Bradyardia/HBE was reported in 24 SGs.[4,6,12,13,26-32] For defining ‘bradyardia/HBE’, primary authors used their own criteria for 8 SGs. The rest followed the definition by Liguori et al.[26] The incidence of isolated bradyardia[12,13,27-30] varied from 0 to 19% ($n = 65$ of 712, 9.1%) and that of HBE[4,6,12,13,26-32] 5 to 28% ($n = 147$ of 988, 14.9% in ISB subjects and $n = 255$ of 1121, 22.7% in ISB and GA subjects).

Meta-analysis of the incidence of bradyardia revealed risk ratio of 9.8 [(RR, 95%CI; 4.4, 21.9), $F = 0\%$, $P < 0.0001$] and HBE, RR of 19.6 [(95%CI; 10.7, 35.8), $F = 0\%$, $P < 0.00001$] in BCP. There was evidence of higher observed ‘excessive risk’ of developing adverse responses for GA subjects over ISB (RD $P < 0.05$, Figure 1).

Primary authors proposed the possible associations of adverse HR-responses with various factors (epinephrine, fentanyl, ISB, norepinephrine, ondansetron or β-adrenergic blockers). Very low evidence was observed to confirm their effects on adverse HR-responses in ISB subjects. However, further analysis revealed that the use of β-adrenergic agonists[4,6,26,32] and fentanyl[12,13,26] did not increase risk of HBEs without its use [test for sub-group difference, $P = 0.29$, $F = 11.4\%$ and $P = 0.45$, $F = 0\%$, respectively (Figure 2)]. Effect of prophylactic ondansetron (4-8 mg) in prevention of HBE was analysed in 2 trials[13,28] meta-analysis revealed OR (non-event, 95%CI) of 4.13 (1.89, 9.02, $P = 0.0004$). Effect of prophylactic use of β-blocker was used in one study[26]; meta-analysis revealed OR (non-event, 95%CI) of 5.8 [1.65, 20.36, $P = 0.006$ (Figure 3)]. In 17 SGs, the timing of bradyardia/HBE was documented. Pooled data showed the timing of occurrence as 33.6 ± 24 minutes.[4,6,12,13,26,28,31] All BCP surgery subjects received midazolam, fentanyl or propofol sedation alone or in combination in ISB group at different doses and timings.

**Second analysis**

**Post-BCP HR responses analysed from serial HR measurements (Figure 4)**

Our meta-analysis of HR-responses over time considered two sub-groups based on the type of anaesthesia and maintenance agents used. BL-HR was reported in 48 SGs ($n = 1334$); 12 used TIVA-propofol[16,33-37] (73.7 ± 13.4 beats/min, $n = 451$), 33 received inhaled anaesthetics[16,29,35,38-50] (73.6 ± 13.6 beats/min, $n = 744$) and 139 subjects had ISB.[6,50] MDs between HR-values at supine (Pre-BCP) and post-BCP status are depicted in Figure 4.

Sensitivity analysis revealed that various anaesthetic agents significantly influenced fall in HRs. However, it made little difference to the overall results when
### Table 1: Summary of results

| Parameter analysis                                                                 | n     | Outcome                                                                                                                                                                                                 | Comments (GRADE recommendation)                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Definition of bradycardia/HBE                                                      | 1121  | Definition of bradycardia/HBE varied much between authors; therefore, the diversified incidence reporting.                                                                                             | Majority of authors used definition by Liguori et al.\(^a\)                                                                                                                                                                   |
| Incidence of bradycardia and anaesthetic influences                                | 712   | 9.1% of subjects are reported with bradycardia with RR of 9.8, after positioning to BCP. It appears that GA was associated with higher (excessive) risk over ISB.                                            | Limited data available for GA subjects; since anaesthetic causes of hypotension incidences are simultaneously included, may over-estimate the true incidences. (\(\oplus\oplus\oplus\oplus\)-low, \(\oplus\oplus\oplus\)-very low, \(\oplus\oplus\oplus\)-moderate; for overall, ISB/SED, GA\& ISB subgroups.)\(^1\) |
| Incidence of HBE and anaesthetic influences                                        | 1121  | 15% of ISB and 23% of GA+ISB subjects are reported with HBE with odds of 30, after positioning to BCP. It appears that GA was associated with higher (excessive) risk over ISB.                             | Limited data available for GA subjects; since anaesthetic causes of hypotension incidences are simultaneously included, may over-estimate the true incidences. (\(\oplus\oplus\oplus\oplus\)-low, \(\oplus\oplus\oplus\)-very low, \(\oplus\oplus\oplus\)-moderate; for overall, ISB/SED, GA\& ISB subgroups.)\(^1\) |
| Timing of bradycardia/HBE                                                          | 848   | Varied significantly in literature; 70% of study groups report the mean timing of adverse HR responses occurring after 30 minutes. Pooled data average timings are 33.6±24 minutes                           | SDs are high for the pooled data                                                                                                                                                                                               |
| Effect of \(\beta\)-agonists (epinephrine) on bradycardia/HBE incidences           | 988   | No evidence of excessive risk of developing HBEs with use of \(\beta\)-agonists compared to subjects without its use.                                                                                     | Epinephrine was used either during ISB local anaesthetic block placement or for saline irrigation fluid of arthroscopy (\(\oplus\oplus\oplus\oplus\)-low; for overall or subgroups analysis)\(^1\) |
| Effect of fentanyl on bradycardia/HBE incidences                                   | 775   | No evidence of excessive risk of developing HBEs with use of fentanyl compared to subjects who did not receive it.                                                                                         | Only the studies which have used fentanyl in every subject, were included for analysis (\(\oplus\oplus\oplus\oplus\)-low, \(\oplus\oplus\oplus\)-high, \(\oplus\oplus\oplus\)-moderate; for overall, and for subgroup analysis, respectively)\(^1\) |
| Effect of prophylactic ondansetron and \(\beta\)-blockers on bradycardia/HBE incidences | 395   | Evidence of lower risk of developing HBE with the use; ondansetron may decrease the incidence by 4 times                                                                                            | Limited number of trials available for \(\beta\)-blocker prophylaxis (\(\oplus\oplus\oplus\)-moderate; for both outcomes)\(^1\)                                                                                                      |
| Serial HR measurements and effect of type of anaesthesia                          | 1453, 1315, 802\(^2\) | Administering GA or GA+ISB is associated with progressive fall of HR over time and this is maximum after 30 minutes under anaesthesia at BCP. Addition of ISB did not cause additional fall in HR. | Pooled measurements were considered                                                                                                                                                                                            |
| Serial HR measurements and effect of maintenance anaesthetic agent                | 1363, 1163, 580\(^3\) | Subjects with TIVA-propofol and ISB subjects had least fall of HR, over time, in BCP.                                                                                                                   | Pooled measurements were considered                                                                                                                                                                                            |
| Serial HR measurements and effect of intraoperative pharmacological agent         | Variable | Evidence of highest fall of HR with the use of fentanyl alone (for mid and delayed HR) or for concomitant use of fentanyl and PVIs (for early) is observed.                                                                 | Limited data is available for fentanyl-PVIs concomitant effects.                                                                                                                                                               |
| Incidence of hypotension and type of anaesthesia (number of subjects)             | 2366  | Evidence of higher ‘excessive’ risk for number of subjects who developed hypotension at BCP for subjects administered with GA over GA+ISB or ISB/SED.                                                                 | Incidences of ‘HBE’ were considered for ISB subjects                                                                                                                                                                           |
| Incidence of hypotension and maintenance anaesthetic agent (number of subjects)   | 1251  | Use of TIVA-propofol was not associated with excessive risk of developing hypotension over inhaled anaesthetics                                                                                           | Few of the TIVA-propofol group subjects had concomitant use of PVIs at the beginning of BCP                                                                                                                                       |
| CDEs and maintenance anaesthetics                                                 | 684   | Maintenance anaesthetics can influence the CDEs; TIVA-propofol was associated with higher ‘excessive’ risks for number of subjects who experienced CDEs than inhalational agents.                                      |                                                                                                                                                                                                                                 |
| CDEs and ISB anaesthesia                                                          | 30    | Shoulder surgeries done under ISB alone was associated with least incidences of CDEs.                                                                                                                                                                             | Only one SG of this meta-analysis has been considered for CDE evaluation. The immediate corrective therapy during a r\(\text{SO}_2\) fall may not reflect the actual differences                                                                 |
| \(\text{rSO}_2\) and maintenance agents (absolute fall)                            | 849   | Absolute fall of \(\text{rSO}_2\) was not influenced by different maintenance anaesthetics; however, a non-statistically significant higher desaturation values were recorded for TIVA-propofol compared to inhaled anaesthesia subjects.  |                                                                                                                                                                                                                                 |

\(^{a}\) Liguori et al. 2017.

\(^{1}\) Limited data available for ISB subgroups.

\(^{2}\) Limited data available for GA subjects.

\(^{3}\) Limited data available for GA subjects; since anaesthetic causes of hypotension incidences are simultaneously included, may over-estimate the true incidences.

\(^{4}\) Limited number of trials available for \(\beta\)-blocker prophylaxis.

\(^{5}\) Limited number of trials available for saline irrigation fluid of arthroscopy.

\(^{6}\) Limited data available for saline irrigation fluid of arthroscopy.

\(^{7}\) Limited data available for saline irrigation fluid of arthroscopy.

\(^{8}\) Limited data available for saline irrigation fluid of arthroscopy.
Table 1: Summary results

| Parameter analysis | n  | Outcome | Comments (GRADE recommendation) |
|--------------------|----|---------|---------------------------------|
| rSO₂ and maintenance agents (lowest achieved) | 599 | Lowest achieved rSO₂ was not influenced by different maintenance agents. However, a non-statistically significant higher desaturation values were recorded for TIVA-propofol compared to inhaled anaesthesia subjects. | The immediate corrective therapy during a rSO₂ fall may not reflect the actual differences |
| rSO₂ - HR relationships | 381 | Meta-correlations reveal that HR measurements from serial recordings of several study groups statistically correlated well with the respective rSO₂ measurements | Statistical correlations were derived from consecutive, serial measurements. |
| SjvO₂ - HR relationships | 186 | Meta-correlations reveal that HR measurements from serial recordings of few study groups statistically correlated well with respective SjvO₂ values | Statistical correlations were derived from consecutive measurements but the strength of correlation was weak. |
| Influence of PVIs on HR | 165 | PVIs did not influence HR fall with in study subjects; however, the magnitude of HR fall was higher compared to control subjects. | Limited data available |
| Influence of PVIs on HR - rSO₂/ SjvO₂ relationships | 90 | PVIs have not influenced the CDEs and HR-rSO₂/SjvO₂ relationships. | Limited data available |
| rSO₂ - MBP relationships | 457 | Meta-correlation analysis revealed a statistically significant correlation between MBP and rSO₂ values | Predictable outcome |
| Vasopressor consumption | 503 | Pooled averages of ephedrine requirements were higher for GA±ISB than GA alone to maintain the desired BP. | Limited data and non-parametric data comparisons. |
| HR of physiological matched controls | 199 | HR increased or remained same in subjects after positioning to BCP. | Physiological controls are those who did not receive any pharmacological agents. |

study controls[29,30,33-35,37,39,43,48-63] and randomised trials[4,6,12,13,15,16,26-30,33-35,37-39,41,42,44-47,50,53-61,64,65] were analysed separately [Table 2]. Meta-regression was performed since primary outcomes, characterised by significant heterogeneity, yielded statistically significant omnibus P values for statistical models considering different maintenance agents and opioids.

With regard to EHR, [6,15,16,26-30,33-35,37-40,42-47,49,51,52,54-58,65,66] and DHR[6,16,29,30,38,41,42,44-47,49,51,55,56,60,61] responses, meta-analysis showed a statistically significant fall in HR in subjects with GA (GA or GA + RA, P < 0.0001). Sensitivity analysis and meta-regressions confirmed that fentanyl significantly influenced the HR drop over time (meta-regression estimates, 14.8, 9.8 and 16.9; standard error (SE) 5.3, 4.3 and 2.8; P = 0.007, 0.024 and <0.001; for early, mid and delayed periods, respectively) in GA subjects (Omnibus P < 0.001. Also, refer ‘publication bias’, Supplementary Digital Content File 5).

Secondary outcomes

BP responses

BP responses were analysed from 67 SGs.[4,6,12,13,15,16,26,38,40,41,44-46,49,56,60,61,64,66] Seven subjects were excluded from the primary study[16,46,58,66] even before surgery due to severe hypotension after BCP. For treatment of hypotension, ephedrine,[16,12,13,16,28,32,35,36,44,45,49,52,60,61] phenylephrine[53,56,60,62,66] or combination of both[29,39,42,46,48,54,59,61,63,65] were used. Less frequently used were cafedrine/theodrenaline,[30,37] ephinephrine,[26,31,43] norepinephrine[64] and metaraminol.[15,50] Number of subjects showing drop in BP was a better predictor for hypotension than absolute values. Supplementary Digital Content File 6 describes the details of hypotension with respect to type of anaesthesia or maintenance agent used at BCP.

CDEs

CDEs were evaluated in 33SGs.[15,16,33-35,39,45,46,48,53,58,61,64,65] Meta-analysis of pooled estimates showed statistically significant fall in absolute values of rSO₂ with both TIVA-propofol[33,35,52,59,61] and inhalational[15,16,33-35,39,45,46,48,53,58,60,64,65] maintenance anaesthetics (P < 0.00001). There were no differences between sub-groups with respect to the type of maintenance agent used (P = 0.05). Lowest recorded values of CDEs[33-35,39,45-47,53,59,60,65] and data on number of subjects who experienced CDEs[16,33,34,39,43,46,59-61,64,65] are detailed in Supplementary Digital Content File 7.
Figure 1: Bradycardia (A) and HBE (B) meta-analysis forest plots. All hypotension incidences were included. BCP – Beach chair position; CI – Confidence interval; GA – General anaesthesia; HBE – Hypotension-bradycardia episode; ISB – Interscalene block; IV- Inverse variance; SE - Standard error
Relationship between rSO\textsubscript{2}, SjvO\textsubscript{2} and HR
Seventeen SGs\cite{33-35,46,56,60,65} evaluated the HR and rSO\textsubscript{2} at specific intervals over the entire BCP period. Data were recorded as statistical averages for absolute values of consecutive timings. Meta-correlation-analysis showed correlation between the HR and rSO\textsubscript{2} values (r = 0.608, 95%CI, 0.439 to 0.735, P < 0.001). Correlation was attempted between HR and SjvO\textsubscript{2} absolute values from 12SGs\cite{16,33,35} Meta-correlation analysis revealed statistically significant but weak parallel correlation (r = 0.397, 95%CI, 0.151 to 0.597, P < 0.001) indicating an association between HR and SjvO\textsubscript{2} values [Figure 5].

Use of PVIs and effect on HR, rSO\textsubscript{2} and HR-rSO\textsubscript{2} relationships\cite{15,33,35} details of physiological controls,\cite{31,53,59,62} vaso-active drugs consumption\cite{16,33,35,40,44,48,54,56,60,62} are detailed elsewhere (Footnote of Supplementary Digital Content File 3).

DISCUSSION
In our meta-analysis, we attempted to find the incidence and associations of adverse HR-responses during shoulder surgeries done in BCP. We observed the incidence of isolated bradycardia and HBE to be 9.1% and 14.9%, respectively. Current literature
provides no concrete evidence linking different anaesthetic techniques, β-agonists or fentanyl with adverse HR-responses. Trials confirming the protective effects of ondansetron and β-blockers against HBEs...
Our meta-analysis unequivocally confirms the influence of fentanyl on HR-drop over time in BCP-GA subjects. Furthermore, HR-rSO₂/SjvO₂ relationships in GA subjects are clearly elucidated. The interpretations of adverse HR events may differ between GA and ISB subjects. The seemingly excessive risk of adverse events for GA over ISB subjects could be fallacious for several reasons. Anaesthetic or sedation related events, differences in incidence reporting among the included studies significantly influenced the data. Several authors have followed the definition of Liguori and colleagues,[26] where hypotension in isolation is considered an ‘adverse event’. Sub-group meta-analysis has excluded ones that may have reported hypotension but not as a ‘true’ event of adverse HR-response. To avoid overlapping terms of these cardiovascular events, we analysed them separately. Any conclusion as to whether the hypotension/HBE event was directly linked to BCP or anaesthetic/non-anaesthetic agents remained elusive after this analysis, since every individual received a pharmacological agent in one form or the other. Inclusion of ISB subjects alone to account for adverse HR-responses was likely to reflect the true incidences. Presuming that every event was not the ‘true’ bradycardia/HBE among all, the actual incidence of bradycardia/HBE therefore, could be less than estimated.

The adverse HR-events were observed approximately between 10 to 50 minutes. Mechanisms related to peak plasma levels of local anaesthetics after ISB or blockade
of cardiac sympathetic nerves via stellate ganglion were described. However, these mechanisms do not explain the adverse HR-responses in GA subjects. The claim in few trials regarding the augmentation of HBE risk by epinephrine has been with very low evidence. Epinephrine was administered either through skin infiltration, saline irrigation, concomitant to local anaesthetic or intra-articular injections. One study compared epinephrine to norepinephrine to study HBEs without a control group. The paucity of data with respect to number of studies or type of drug (local anaesthetics, beta-agonists etc.) poses a limitation to any conclusion regarding risk modifying drugs. The factors like variable plasma levels with different routes of administration, short half-life etc., will not favour the specific timings of adverse events. Furthermore, we could not demonstrate higher incidences of adverse HR-responses for the fentanyl SGs over no-fentanyl in ISB subjects. Earlier studies have reported a dose-dependent increase in bradycardia/HBE incidences with fentanyl in BCP-cohorts. The effects of fentanyl on HR were further validated by our second analysis of this study as we observed the highest HR-fall occurring with the use of fentanyl. Fentanyl acts on μ-opioid receptors on cardiac vagal neurons in the nucleus ambiguus and neurons preceding them to reduce GABAergic neurotransmission and induce bradycardia. We believe, therefore, that adverse HR-response could be easily augmented with fentanyl use.

Association between CDEs and HR is as yet unreported. While HR is believed to be influenced by hypoxic events, defining HR-rSO subscript 2 relationship is not easy. Cerebral oxygenation may involve regional differences. The near-infrared reflectance spectroscopy is usually applied to frontal areas for convenience while actual rSO subscript 2 at the medullary vasomotor centre (VMC) is un-monitored. We have demonstrated a HR-rSO subscript 2/SjvO subscript 2 association through meta-correlation analysis. There is a
dearth of literature on monitoring rSO$_2$ during the ISB-BCP surgery with none reporting any adverse HR-responses. CDEs in ISB-BCP patients have been reported as incidences of 10% [67] or 3.3% [56] or lower absolute values of rSO$_2$ [60]. Higher partial pressures of oxygen during controlled ventilation may decrease the CDEs compared to spontaneously breathing (but sedated) ISB subjects. CDEs reported by Yadeau and colleagues [67] in RA patients showed no correlation with all hypotensive events. All ISB studies reporting bradycardia/HBE received intravenous fentanyl and midazolam singly or in combination. Furthermore, propofol infusion (sedation), β-blockers and oxygen (discretional) were randomly used in ISB subjects of this meta-analysis. Adverse HR-responses observed in ISB subjects, therefore, could be secondary to sedation and its CDE effects. [60]

We have limitations for our meta-analysis. From the available studies, we were unable to describe emergent strategy for preventing and managing adverse HR-responses during BCP-surgery, which is needed to inform practice. Non-availability of raw patient data or lowest achieved HR data for many trials precluded conducting individual patient meta-analysis or correlations. Heterogeneity is high in our study but we consider this acceptable since the pre-defined eligibility criteria for the meta-analysis are sound and the data are correct. While included trials might have allocated treatment randomly, their SGs inclusion in this review has not been random. Publication bias was minimal. However, inclusions of studies to this review were not based on Jadad scores.

CONCLUSIONS

Amalgamating the diverse and selective reporting of HR-responses in literature on shoulder surgeries in BCP, we observed lack of enough evidence for definitive associations of adverse HR-responses with different pharmacological agents like β-agonists or opioids. However, fentanyl can significantly influence HR-fall in BCP. Since HR-variations correlate well with monitored brain saturation values, the adverse HR-responses may also be induced by regional oxygenation of VMC in the brain, independent of anaesthetic agents. Close monitoring for CDEs could free the anaesthesiologist from concerns regarding the type of anaesthesia as well as intra-operative maintenance anaesthetic agents and ancillary drugs employed. However, further studies are essential to derive a cause-effect relationship with respect to adverse HR-responses. The key may lie in cerebral oxygenation levels at the VMC, and monitoring this parameter could set the direction for future research in this field.

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Conflicts of interest

There are no conflicts of interest.

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|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
|1 | Beach chair position | 33 | Hypotensive bradycardic episode | 58 | Bezold jarisch reflexes |
|2 | Beach-chair position | 34 | Hypotensive bradycardic episodes | 59 | Bezold jarisch response |
|3 | BCP | 35 | Hypotensive bradycardic events | 60 | Bezold jarisch s |
|4 | BCP complication | 36 | Bradycardic episode | 61 | OR/38 to 53 (377) |
|5 | BCP complications | 37 | OR/31 to 36 (37) | 62 | Bradycardia |
|6 | BCP anaesthesia | 38 | Bezold jarish reflex | 63 | Bradycardia/arrest |
|7 | BCP anaesthesia | 39 | Bezold jarish reflex activation | 64 | Bradycardia/asystole |
|8 | Beach chair seated positioning | 40 | Bezold jarisch like bradycardia reflex | 65 | Bradycardia/asystolia |
|9 | Beach chair seated anaesthesia | 41 | Bezold jarish | 66 | Bradycardia/asystolic |
|10 | Beach chair seated surgery | 42 | Bezold jarisch like bradycardia reflex | 67 | Bradycardia/atrioventricular |
|11 | OR/1 to 10 (3235) | 43 | Bezold jarisch reflex like reaction | 68 | Bradycardia/bradyarrhythmia |
|12 | Shoulder arthroscopy | 44 | Bezold jarisch effects | 69 | Bradycardia/cardiac |
|13 | Shoulder arthroplasty | 45 | Bezold jarisch like | 70 | Bradycardia/case |
|14 | Shoulder arthroscopic surgery | 46 | Bezold jarisch like bradycardia reflex | 71 | Bradycardia/complications |
|15 | Shoulder surgery | 47 | Bezold jarisch like effect | 72 | Bradycardia/collapse |
|16 | Shoulder scopy | 48 | Bezold jarisch like phenomenon | 73 | Bradycardia/desaturation |
|17 | OR/12 to 16 (37477) | 49 | Bezold jarisch like reflex | 74 | Bradycardia/hypotension |
|18 | Hemodynamic | 50 | Bezold jarisch model | 75 | Bradycardia/sinus |
|19 | Hemodynamic monitoring | 51 | Bezold jarisch reflex | 76 | Bradycardia/sinus arrest |
|20 | Hemodynamic/clinical | 52 | Bezold jarisch reflex activation | 77 | Bradycardia/slow |
|21 | Hemodynamic/anaesthetic | 53 | Bezold jarisch reflex assay | 78 | Bradycardia/surgery |
|22 | Hemodynamic | 54 | Bezold jarisch reflex function | 79 | Bradycardia/event |
|23 | Haemodynamic monitoring | 55 | Bezold jarisch reflex induced decrease | 80 | Bradycardia events |
|24 | OR/18 to 23 (724087) | 56 | Bezold jarisch reflex responses | 81 | OR/62 to 80 (25618) |
|25 | Heart rate | 57 | Bezold jarisch reflex test | 82 | Epinephrine |
|26 | Heart rate response |   |   | 83 | Adrenaline |
|27 | Heart rate responses |   |   | 84 | Beta blocker |
|28 | Adverse hemodynamic events |   |   | 85 | Ondansetron |
|29 | Adverse heart rate response |   |   | 86 | 11 OR 17 OR 24 OR 30 OR 37 OR 61 OR 81 (909292) |
|30 | OR/25 to 29 (338011) |   |   | 87 | 17 AND 37 AND 61 (2289) |
|31 | Hypotensive bradycardic episode |   |   | 88 | 11 AND 17 (214) |
|32 | Hypotensive bradycardic |   |   | 89 | 17 AND 81 (45) |
|   |   |   |   | 90 | 17 AND 30 (181) |
|   |   |   |   | 91 | 11 AND 24 (41) |
|   |   |   |   | 92 | 61 AND 81 (118) |

**Supplementary Digital Content File 1:** The Search Strategy. The search terms were used to search databases of MEDLINE, EMBASE, CCRCT and, CINHAL (modified to suit each specific database with abstract, keywords and text with the removal of duplicates).
Supplementary Digital Content File 2: Flow Chart for literature Identification and Study Selection. Details of analysis and outcomes are shown.

BCP - Beach chair position; CDE - Cerebral desaturation event; GA - General anaesthesia; HR - Heart rate; HBE - Hypotension-bradycardia episode; ISB - Interscalene block; PVIs - Prophylactic vasopressor infusions; rSO$_2$ - Regional cerebral oxygen saturation; TIVA - Total intravenous anaesthesia
### Supplementary Digital Content File 3: Characteristics of included study groups

ASA PS - American Society of Anaesthesiologists Physical Status; AVP - Arginine vasopressin; BCP - Beach chair position; BIS - Bispectral index; BL - Baseline; BP - Blood pressure; CVS - Cardiovascular system; CBF - Cerebral blood flow; DM - Diabetes mellitus; E - Epinephrine; Eph - Ephedrine; ES - Elastic stockings; GA - General anaesthesia; HBE - Hypotension bradycardia episode; HES - Hydroxyethyl starch; HR - Heart rate; HTN - Hypertension; IOP - Intraocular pressure; ISB - Interscalene block; LA - Local anaesthetics; MAP - Mean arterial pressure; MBP - Mean blood pressure; MCA - Middle cerebral artery; N2O - Nitrous oxide; NA - not applicable; NE - Norepinephrine; NIRS - Near-infrared spectroscopy; NP - Not provided; NS - Normal saline; O2 - Oxygen; Phe - Phenylephrine; PNS - Peripheral nerve stimulator; PR - Propofol remifentanil; RL - Ringer lactate; SBP - Systolic blood pressure; SCD - Sequential compression device; SN - Sevoflurane nitrous oxide; SG - Study group; TCI - Target controlled infusion; TIVA - Total intravenous anaesthesia; USG - Ultrasound guided.

- per subject
- average incidence per subject in a SG
- Liguori et al., defined HBE as HR <50 beats/min at anytime or <30 beats in less than 5 minutes compared to pre-anaesthetic state with or without hypotension, and/or decrease in SBP >30 mmHg in <5 min compared to pre-anaesthetic values, or any SBP decrease <90 mm Hg; necessarily treated by ephedrine, epinephrine or atropine.
- pooled data. *only mean value is provided. **interventions per subject

| Year | SG | Characteristics | Notes |
|------|----|----------------|-------|
| 2011 | 1  | ... | ... |
| 2012 | 2  | ... | ... |
| 2013 | 3  | ... | ... |
| 2014 | 4  | ... | ... |
| 2015 | 5  | ... | ... |

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| Year | SG | Characteristics | Notes |
|------|----|----------------|-------|
| 2011 | 1  | ... | ... |
| 2012 | 2  | ... | ... |
| 2013 | 3  | ... | ... |
| 2014 | 4  | ... | ... |
| 2015 | 5  | ... | ... |

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| Year | SG | Characteristics | Notes |
|------|----|----------------|-------|
| 2011 | 1  | ... | ... |
| 2012 | 2  | ... | ... |
| 2013 | 3  | ... | ... |
| 2014 | 4  | ... | ... |
| 2015 | 5  | ... | ... |
Note (Supplementary Digital Content File 3):

**Analysis details:** Data of studies which include both analysis; (1) HR data of adverse HR-responses (first analysis); (2) HR data of HR-variability (second analysis). To define an ‘adverse event’, authors’ own definitions have been used. Details of bradycardia/HBE or hypotension are shown in separate columns.

During second analysis of HR variabilities, we found no publication bias for EHR and DHR (Egger’s test, \( P = 0.836 \) and 0.976, respectively) for included studies. However, funnel plot showed that the study by Meex et al.,\[59\] influenced the analysis (Egger’s test, \( P < 0.001 \)). Excluding this study resulted in non-significant \( P \) value (\( P = 0.06 \)) for MHR responses. However, inclusion of this study did not alter the overall outcomes for MHRs. Please see Supplementary Digital Content File 5 for ‘Publication bias’.

**Use of prophylactic vasopressor infusions (PVIs) and effect on HR, rSO\(_2\) and HR-rSO\(_2\) relationships:** PVIs were used in 10 SGs. The certainty of the effects of PVIs on HR necessitated additional analyses on the control groups of each trial. Meta-analysis clearly demonstrated lower HR in BCP among SGs using PVIs as compared to those not using them (\( P = 0.004 \), within trials).\[15,33-35\] When SGs using PVIs were compared in pre- and post-BCP, lower HRs were not observed (\( P = 0.23 \), within SGs).\[15,33-35\] The overall association of PVIs vis-à-vis HR changes in BCP was non-significant (sensitivity analysis and meta-regression). Since we considered rSO\(_2\) values for the entire duration of surgery, no attempt was made to establish relationships between the two. Further, meta-correlation analyses were considered on HR-rSO\(_2\) relationships with and without use of PVIs. The use of PVIs did not make a difference (with PVIs use, \( r = 0.693 \), 95%CI, 0.391 to 0.860, \( P < 0.001 \), random effects, \( F = 72.5\%\), \( n = 90 \) and without PVIs use, \( r = 0.560 \), 95%CI, 0.332 to 0.727, \( P < 0.001 \), random effects, \( F = 80.81\%\), \( n = 291 \)).

**Relationship between rSO\(_2\) and MBP:** Twenty SGs\[16,33-35,46,56,60,65\] evaluated MBP and rSO\(_2\) at specific intervals over the entire BCP period. Data were recorded as statistical averages for absolute values of consecutive timings. Meta-correlation analysis showed statistically significant correlation between MBP and rSO\(_2\) values (\( r = 0.597 \), 95% CI, 0.432 to 0.723, \( P < 0.001 \), random effects, \( F = 79.9\%\)) confirming the predictable relationship between the two.

**Physiological controls and HR:** Four SGs\[31,53,59,62\] evaluated HR responses over time. Meta-analysis demonstrated no change of HR after positioning to BCP (\( P = 0.58 \)).

**Vaso-active drugs consumption:** Pooled averages of ephedrine requirements (mgs) were higher for GA ± ISB (\( n = 83 \)) subjects\[54,56\] than GA alone\[16,33,35,46,48,60,62\] (\( n = 390 \)) to maintain the desired BP (23.1 ± 32.1 vs 15.4 ± 27.3, per subject, respectively, \( P = 0.026 \)). Ephedrine consumptions in inhalation anaesthesia\[16,35,40,44,48,54,60\] (\( n = 396 \)) and TIVA-propofol\[16,33,35\] (\( n = 77 \)) were 17.8 ± 31.1 and 12.4 ± 5.9 respectively (\( P = 0.236 \)). CDEs, rSO\(_2\) and HR measurements were not analysed for vaso-active drug consumptions as the timings of administration were inadequately available.

**Jadad scores:** Variable Jadad scores (-2 to 5) were observed for included studies as inclusion of studies to this meta-analysis was not set for minimum scores. Inclusion of all studies would not change the incidences of adverse HR-responses. This is because all subjects of BCP-surgery were analysed pre– and post-BCP status in addition to comparative controls during analysis.

BCP - Beach chair position; BP - Blood pressure; CDE - Cerebral desaturation event; CI - Confidence intervals; DHR - Delayed heart rate; EHR - Early heart rate; GA - General anaesthesia; HBE - Hypotension bradycardia episode; HR - Heart rate; ISB - Interscalene block; MBP - Mean blood pressure; MHR - Mid heart rate; PVI - Prophylactic vasopressor infusion; rSO\(_2\) - regional cerebral oxygen saturation; SG - Study group; TIVA - Total intravenous anaesthesia.
Supplementary Digital Content File 4: Risk of bias summary (a) and graph (b)
| No. | Parameter                        | Inclusion of Meex et al,^[59] | Excluding Meex et al,^[59] |
|-----|---------------------------------|-------------------------------|---------------------------|
| 1   | HR fall (beats/min)             |                               |                           |
|     | Type of anaesthesia, MD (95% CI)| 4.5 (2.9, 6.2)                | 4.2 (2.9, 5.4)            |
|     | Test for heterogeneity          | $I^2 = 69\%, P < 0.00001$    | $I^2 = 40\%, P < 0.004$   |
|     | Test for subgroup differences   | $P = 0.28$                   | $P = 0.33$               |
| 2   | HR fall (beats/min)             |                               |                           |
|     | Maintenance agent, MD (95% CI) | 4.9 (3.06, 6.73)              | 4.5 (3.6, 5.9)           |
|     | Test for heterogeneity          | $I^2 = 70\%, P < 0.00001$    | $I^2 = 43\%, P < 0.002$  |
|     | Test for subgroup differences   | $P = 0.15$                   | $P < 0.0001$             |
| 3   | CDEs (Incidence, log-number of subjects) |                 |                           |
|     | Maintenance agent, MD (95% CI) | 0.31 (0.19, 0.42)             | 0.29 (0.17, 0.41)        |
|     | Test for heterogeneity          | $I^2 = 94\%, P < 0.00001$    | $I^2 = 94\%, P < 0.00001$|
|     | Test for subgroup differences   | $P = 0.006$                  | $P = 0.02$               |
| 4   | rSO₂ (absolute fall, %)        |                               |                           |
|     | Maintenance agent, MD (95% CI) | 6.3 (4.9, 7.6)                | 6 (4.6, 7.3)             |
|     | Test for heterogeneity          | $I^2 = 72\%, P < 0.00001$    | $I^2 = 63\%, P < 0.00001$|
|     | Test for subgroup differences   | $P = 0.052$                  | $P = 0.13$               |
| 5   | rSO₂ (lowest achieved, %)      |                               |                           |
|     | Maintenance agent, MD (95% CI) | 9.3 (6.7, 11.8)               | 8.7 (7, 10.3)            |
|     | Test for heterogeneity          | $I^2 = 90\%, P < 0.00001$    | $I^2 = 72\%, P < 0.00001$|
|     | Test for subgroup differences   | $P = 0.22$                   | $P = 0.26$               |

Supplementary Digital Content File 5: Publication Bias. All the measures are MDs from pre- to post-BCP status. HR was considered for mid periods (11-30 mins of BCP) only as data for rest of the periods (EHR and DHR) did not reveal publication bias during funnel plot asymmetry evaluation and Egger's test. We observe after inclusion of study by Meex et al,[59] there are no gross change in the results for most of the parameters indicating addition of this study had not influenced the data outputs. CDE - Cerebral desaturation event; CI – Confidence interval; HR - Heart rate; MD – Mean difference; rSO₂ - Regional cerebral oxygen saturation
Supplementary Digital Content 6: The figure that illustrates the forest plot depicting number of subjects experiencing the hypotension episodes with respect to (a) Type of anaesthesia (GA, GA + ISB or ISB ± sedation) (b) Maintenance agent (TIVA-propofol or inhaled anaesthesia). Meta-analysis of this parameter for pre- and post-BCP status revealed higher RD for SGs with GA than GA + ISB subjects and ISB ± sedation ($P_{\text{sub-group differences}} = 0.0007$, $I^2 = 86.2\%$). However, higher observed risk was not found for subjects of TIVA-propofol over inhaled anaesthetics for developing hypotensive responses ($P = 0.76$, $I^2 = 0\%$). BCP - Beach chair position; CI - Confidence interval; GA - General anaesthesia; ISB - Interscalene block; IV - Inverse variance; RD - Risk difference; SE - Standard error; SG - Study group; TIVA - Total intravenous anaesthesia.
Supplementary Digital Content File 7: The figure that illustrates the number of subjects who experienced regional CDEs. (a) Meta-analysis of pooled estimates showed statistically significant fall in absolute values of rSO$_2$ with both TIVA-propofol and inhalational maintenance anaesthetics ($F = 72\%$, $P < 0.00001$). In 4 SGs which had separate left and right cerebral hemisphere recordings, the readings of the side with maximum MDs were considered. There were no differences between sub-groups with respect to the type of maintenance agent used ($F = 74.4\%$, $P = 0.05$). Type of anaesthesia (GA or GA + ISB) was not considered for sub-group evaluation due to paucity of relevant publications. There was no evidence of publication bias (Egger’s test, $P = 0.466$). (b) Lowest recorded values of CDEs were extracted from 23 SGs. Lowest MD values of CDEs, showed no sub-group differences between different maintenance agents ($F = 74\%$, $P = 0.22$) over 5 to 90 minutes or till the end of surgery, whichever was earlier. There was evidence of publication bias (Egger’s test, $P = 0.003$) however without affecting overall results (refer ‘publication bias’, Supplementary Digital Content File 5). (c) Number of subjects who experienced CDEs were reported in 24 SGs. Sub-group analysis of number of subjects who experienced CDEs revealed that TIVA-propofol had higher RD ($F = 74\%$, $P = 0.22$) over 5 to 90 minutes or till the end of surgery, whichever was earlier. There was no evidence of publication bias (Egger’s test, $P = 0.257$). BCP - Beach chair position; CDE – Cerebral desaturation event; CI - Confidence interval; IV - Inverse variance; ISB – Interscalene block; rSO$_2$ - Regional cerebral oxygen saturation. SE - Standard error; TIVA - Total intravenous anaesthesia.