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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> Submitted: 10-Mar-2020 Revised: 02-May-2020 Accepted: 07-Jul-2020 Published: 31-Jul-2020

Access	this	article	online

Website: www.ijaweb.org

DOI: 10.4103/ija.IJA_228_20

Quick response code



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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, guasi-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 β -agonists did not increase risk of HBEs (P = 0.29, $l^2 = 11.4\%$) or with fentanyl (P = 0.45, $l^2 = 0\%$) 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, $\ell = 86.7\%$). Meta-correlation analysis showed relationships between the HR and rSO₂ (regional cerebral oxygen saturation) or SjvO₂ (jugular venous oxygen saturation) values (r = 0.608, 95%CI, 0.439 to 0.735, P < 0.001, $l^2 = 77.4\%$ and r = 0.397, 95%CI, 0.151 to 0.597, P < 0.001, $l^2 = 64.3\%$, respectively). **Conclusions:** There is not enough evidence

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How to cite this article: Tantry TP, Karanth H, Koteshwar R, Shetty PK, Adappa KK, Shenoy SP, *et al.* Adverse heart rate responses during beach-chair position for shoulder surgeries - A systematic review and meta-analysis of their incidence, interpretations and associations. Indian J Anaesth 2020;64:653-67.

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to claim the associations of adverse HR-responses with any specific factor. HR-fall is maximal with fentanyl and its variability is associated with changes in rSO_2 . Fall in rSO_2 could be the common link triggering adverse HR-responses in BCP.

Level and Quality of Evidence: Level of evidence, IIA/IIB; GRADE recommendation, B.

Key words: Adrenergic beta-receptor agonists, arthroscopy, bradycardia, fentanyl, oximetry, shoulder, sitting position

INTRODUCTION

undesirable haemodynamic Among the 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.^[1-4] A specifically named haemodynamic event, the 'Hypotension-Bradycardia Episode' (HBE) has been reported in 6-27% of BCP subjects.^[3-5] 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,^[4,6] 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^[5] or the anaesthetic agent deployed has not been conclusively established.^[7] 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,^[8] the demonstration of a 'non-empty' heart ventricle during such events suggests otherwise.^[9-11] Similarly, the association of use of β -adrenergic agonists and adverse heart rate (HR)-responses/HBE^[2,4] is uncertain since these episodes were also reported in patients without their use.^[12,13] Likewise, while ISB has been linked to such events,^[8] 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)^[14-16] and jugular venous oxygen saturation $(SjvO_2)$ for BCP surgeries done under anaesthesia.^[16] 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 for bradycardia/HBEs 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.^[17] 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 $<45^{\circ}$ 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 ($\geq 45^{\circ}$ 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-rSO₂/SjvO₂ associations. The latter included incidence and magnitude of hypotension and associations of mean blood pressure (MBP) with anaesthetic factors, vasoactive drugs and rSO₂/SjvO₂ 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 (Enguage 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 $\sqrt{[(\Sigma N^* SD^2)/\Sigma N]}$ 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 Hand Book.^[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 complicationsrelated 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 incidence of hypotension in the supine position under anaesthesia. Subjects who were excluded prior to surgery, after BCP, owing to severe hypotension were also included (intention to treat).

Data synthesis specific to CDEs

For analysing CDEs, two types of 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 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 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 \pm 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 version 0.9.2).^[25] Correlations software, were attempted for those SGs which mentioned statistical averages of consecutive measurements of HR, rSO, 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 byba, 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)^[26] was included against the PRISMA protocol, as the same was used by the rest of the authors to define HBE.

First analysis

Bradycardia and/or HBE

Bradycardia/HBE was reported in 24 SGs.^[4,6,12,13,26-32] For defining 'bradycardia/HBE', primary authors used their own criteria for 8 SGs. The rest followed the definition by Liguori *et al.*^[26] The incidence of isolated bradycardia^[12,13,27-30] varied from 0 to 19% (n = 65 of 712, 9.1%) and that of HBE,^[4,6,12,13,26,28-32] 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 bradycardia revealed risk ratio of 9.8 [(RR, 95%CI; 4.4, 21.9), $I^2 = 0\%$, P < 0.0001] and HBE, RR of 19.6 [(95%CI; 10.7, 35.8), $I^2 = 0\%$, 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).

authors Primary 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^[12,13,28] did not increase risk of HBEs without its use [test for sub-group difference, P = 0.29, $I^2 = 11.4\%$ and P = 0.45, $I^2 = 0\%$, 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 bradycardia/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

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		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 <i>et al.</i> ^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.	Limited data available for GA subjects $(\oplus \oplus \oplus \odot$ -moderate, for overall and all subgroups) ^f
		ISB had no excessive risk of developing bradycardia over GA.	
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. $(\oplus \oplus \bigcirc \bigcirc -$ low, $\oplus \bigcirc \bigcirc \bigcirc -$ very low, $\oplus \oplus \oplus \bigcirc -$ moderate; for overall, ISB±sedation, GA±ISB subgroups.) ^f
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 β-agonists (epinephrine) on bradycardia/HBE incidences	988	No evidence of excessive risk of developing HBEs with use of β -agonists compared to subjects without its use.	Epinephrine was used either during ISB local anaesthetic block placement or for saline irrigation fluid of arthroscopy $(\oplus \oplus \bigcirc \bigcirc -$ low; for overall or subgroups analysis) ^f
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 ($\oplus \oplus \odot \bigcirc$ -low, $\oplus \oplus \oplus \oplus$ -high, $\oplus \oplus \oplus \bigcirc$ -moderate; for overall, and for subgroup analysis, respectively)
Effect of prophylactic ondansetron and $\beta\text{-blockers}$ 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 β -blocker prophylaxis ($\oplus \oplus \oplus \odot$ -moderate; for both outcomes) ^f
Serial HR measurements and effect of type of anaesthesia	1453, 1315, 802⁵	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°	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±sedation.	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.
rSO ₂ and maintenance agents (absolute fall)	849	Absolute fall of 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.	The immediate corrective therapy during a rSO ₂ fall may not reflect the actual differences

		Table 1: Summary results	
Parameter analysis	n	Outcome	Comments (GRADE recommendation)
rSO ₂ and maintenance agents (lowest achieved)	599	Lowest achieved rSO ₂ 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 rSO ₂ fall may not reflect the actual differences
rSO ₂ - HR relationships	381	Meta-correlations reveal that HR measurements from serial recordings of several study groups statistically correlated well with the respective rSO ₂ measurements	Statistical correlations were derived from consecutive, serial measurements.
SjvO ₂ - HR relationships	186	Meta-correlations reveal that HR measurements from serial recordings of few study groups statistically correlated well with respective SjvO ₂ 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 -rSO ₂ / SjvO ₂ relationships	90	PVIs have not influenced the CDEs and HR-rSO ₂ /SjvO ₂ relationships.	Limited data available
rSO ₂ ² - MBP relationships	457	Meta-correlation analysis revealed a statistically significant correlation between MBP and rSO ₂ values	Predictable outcome
Vasopressor consumption ^d	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 ^e	HR increased or remained same in subjects after positioning to BCP.	Physiological controls are those who did not receive any pharmacological agents.

Assessment, Development and Evaluation; HBE – Hypotension bradycardia episode; HR – Heart rate; ISB – Interscalene block; MBP – Mean blood pressure; PVI – Prophylactic vasopressor infusion; rSO₂ – Regional oxygen saturation of brain; SD – Standard deviation; SjvO₂ – Jugular venous oxygen saturation; TIVA – Total intravenous anaesthesia; "Liguori *et al.*, defined HBE as HR <50 beats/min at anytime or <30 beats in <5 min 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 mmHg; necessarily treated by ephedrine, epinephrine or atropine. ^bcdata for early, mid and delayed heart rate ^aequivalent doses ^edata not included for total *n* of meta-analysis. 'GRADE for primary outcomes

study controls^[29,30,33-35,37,39-43,48-63] and randomised trials^[4,6,12,13,15,16,26-30,33-35,37-39,41,42,44-47,50,55,60,61,64] 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,^[6,15,16,29,33-35,37-40,42-47,49,51,52,54-58,65] MHR^{[16},^{29,33-36,38,41,43,46,48-51,53-64,66]} and DHR^{[6,16,29,30,38,43,46,47,49,51,55,5},^{6,60,65]} 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. $^{[4,6,12,13,15,16,2]}_{8\cdot 38,40,41,44\cdot 46,49\cdot 56,60,61,64,66]}$ 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,^[4,6,12,13,16,28,32,35,36,44,45,49,52,60] 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] epinephrine,^[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 maintainance 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^[15,16,35,39,45,46,48,53,58,60,64,65] 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^[6,33,34,39,43,46,59-61,64,65] are detailed in Supplementary Digital Content File 7.

4	Study or Subgroup 1.1.1 ISB ± sedation	Risk Difference	SE	Supine Total		Weight	Risk Difference IV, Random, 95% Cl	Risk Difference IV, Random, 95% Cl
	Hasanein a] 2014	0 0204	0.0279	49	49	8.7%	0.02 [-0.03, 0.08]	_ _
	Hasanein b] 2014		0.0332	50	50	7.9%	0.04 [-0.03, 0.11]	+ -
	Hasanein c] 2014		0.0464	49	49	6.0%	0.10 [0.01, 0.19]	
	Nallam a] 2015		0.0464	49	49	6.0%	0.10 [0.01, 0.19]	
	Nallam b] 2015		0.0279	49	49	8.7%	0.02 [-0.03, 0.08]	- -
	Sia 2003		0.0317	110	110	8.1%	0.12 [0.06, 0.18]	
	Song a] 2011		0.0242	40	40	9.3%	0.00 [-0.05, 0.05]	
	Song b]2011		0.0559	40	40	4.9%	0.13 [0.02, 0.23]	
	Song c] 2011		0.0469	40	40	5.9%	0.07 [-0.02, 0.17]	+
	Song d] 2011		0.0242	40	40	9.3%	0.00 [-0.05, 0.05]	
	Subtotal (95% CI)	v	0.0212	516	516	74.8%	0.05 [0.02, 0.08]	•
	Heterogeneity: Tau ² = Test for overall effect:			P = 0.03);	l ² = 53%	/6		
	1.1.2 GA ± ISB							
		0.04	0.0521	25	25	E 20/	0.04 [0.06 0.14]	
	Jang a] 2016		0.0531 0.0638	25 25	25 25	5.2%	0.04 [-0.06, 0.14]	
	Jang b] 2016					4.2%	0.08 [-0.05, 0.21]	
	Jansen a] 2014 Jansen b] 2014		0.0629 0.0547	42 41	42 41	4.2% 5.0%	0.19 [0.07, 0.31]	
	Oh a]2019		0.0547	34	34	3.2%	0.12 [0.01, 0.23] 0.26 [0.11, 0.42]	
	Oh aj2019 Oh bj2019		0.0778	34 29	34 29	3.2%	0.26 [0.11, 0.42]	
	Subtotal (95% CI)	0.1724	0.0744	196	196	25.2%	0.13 [0.07, 0.20]	-
	Heterogeneity: Tau ² = Test for overall effect:						0.10[0.07, 0.20]	•
	Total (95% CI)			712		100.0%	0.07 [0.04, 0.10]	
	Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diffe	Z = 4.50 (P < 0.00	001)					-0.2 -0.1 0 0.1 0.2 Supine BCP
				Supine			Risk Difference	Risk Difference
5	Study or Subgroup	Risk Difference	SE			Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% Cl
3	Study or Subgroup 1.2.1 ISB ± sedation	Risk Difference	SE			Weight		
3			SE 0.0577			Weight 4.5%		
3	1.2.1 ISB ± sedation	0.2542		Total	Total		IV, Random, 95% CI	
3	1.2.1 ISB ± sedation Chierichini a] 2015	0.2542 0.0833	0.0577	Total 59	Total 59	4.5%	IV, Random, 95% Cl 0.25 [0.14, 0.37]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015	0.2542 0.0833 0.0612	0.0577 0.0384	Total 59 60	Total 59 60	4.5% 4.6%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16]	
8	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014	0.2542 0.0833 0.0612 0.06	0.0577 0.0384 0.0387	Total 59 60 49	Total 59 60 49	4.5% 4.6% 4.6%	IV, Random, 95% CI 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14]	
8	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014	0.2542 0.0833 0.0612 0.06 0.2041	0.0577 0.0384 0.0387 0.038	Total 59 60 49 50	Total 59 60 49 50	4.5% 4.6% 4.6% 4.6%	IV, Random, 95% CI 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014	0.2542 0.0833 0.0612 0.06 0.2041 0.2813	0.0577 0.0384 0.0387 0.038 0.0593	Total 59 60 49 50 49	Total 59 60 49 50 49	4.5% 4.6% 4.6% 4.6% 4.5%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32]	
8	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766	0.0577 0.0384 0.0387 0.038 0.0593 0.057	Total 59 60 49 50 49 64	Total 59 60 49 50 49 64	4.5% 4.6% 4.6% 4.5% 4.5%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536	0.0577 0.0384 0.0387 0.038 0.0593 0.057 0.0665 0.0341	Total 59 60 49 50 49 64 47	Total 59 60 49 50 49 64 47	4.5% 4.6% 4.6% 4.5% 4.5% 4.5%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998	0.2542 0.0833 0.0612 0.2041 0.2813 0.2766 0.0536 0.2174	0.0577 0.0384 0.0387 0.038 0.0593 0.057 0.0665 0.0341 0.0626	Total 59 60 49 50 49 64 47 56	Total 59 60 49 50 49 64 47 56	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998 Nallam a] 2015	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245	0.0577 0.0384 0.0387 0.038 0.0593 0.057 0.0665 0.0341	Total 59 60 49 50 49 64 47 56 46	Total 59 60 49 50 49 64 47 56 46	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612	0.0577 0.0384 0.0387 0.038 0.0593 0.057 0.0665 0.0341 0.0626 0.0612	Total 59 60 49 50 49 64 47 56 46 46 49	Total 59 60 49 50 49 64 47 56 46 46 49	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.5%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.00512	0.0577 0.0384 0.0387 0.038 0.0593 0.057 0.0665 0.0341 0.0626 0.0612 0.0387	Total 59 60 49 50 49 64 47 56 46 49 49	Total 59 60 49 50 49 64 47 56 46 46 49 49	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.29 [0.17, 0.41]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori c] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.0612 0.1091 0.2909	0.0577 0.0384 0.0387 0.038 0.0593 0.057 0.0665 0.0341 0.0626 0.0612 0.0387 0.0446	59 60 49 50 49 64 47 56 46 49 49 49 55	Total 59 60 49 50 49 64 47 56 46 49 49 55	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.29 [0.17, 0.41]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1	0.0577 0.0384 0.0387 0.038 0.0593 0.057 0.0665 0.0341 0.0626 0.0612 0.0387 0.0446 0.0622	Total 59 60 49 50 49 64 47 56 46 49 55 55	Total 59 60 49 50 49 64 47 56 46 49 55 55	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori a] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003 Song a] 2011 Song b] 2011	0.2542 0.0833 0.0612 0.2041 0.2041 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2090 0.1	0.0577 0.0384 0.0387 0.0593 0.057 0.0665 0.0341 0.0626 0.0387 0.0446 0.0622 0.0517	59 60 49 50 49 64 47 56 46 49 49 55 55 40	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori a] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003 Song a] 2011 Song b] 2011 Song c] 2011	0.2542 0.0833 0.0612 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35	0.0577 0.0384 0.0387 0.0593 0.057 0.0665 0.0341 0.0662 0.0387 0.0446 0.0622 0.0446 0.0622	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 55 55 40 40	Total 59 60 49 50 49 64 47 56 46 49 55 55 40 40	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.6% 4.4%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.17, 0.39] 0.28 [0.17, 0.34] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori a] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003 Song a] 2011 Song b] 2011	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.35	0.0577 0.0384 0.0387 0.0593 0.0593 0.0665 0.0341 0.0665 0.0612 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 55 50 40 40	Total 59 60 49 50 49 64 47 56 46 49 55 55 40 40 40	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.17, 0.39] 0.22 [0.09, 0.34] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.11 [0.02, 0.20] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003 Song a] 2011 Song b] 2011 Song c] 2011	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.35	0.0577 0.0384 0.0387 0.0593 0.0575 0.0665 0.0341 0.0626 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766 0.0766 0.07411	Total 59 60 49 50 49 64 47 56 46 47 56 46 49 49 55 55 40 40 40 40	Total 59 60 49 50 49 60 49 64 47 56 46 49 55 55 50 40 40 40 40	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.17, 0.39] 0.28 [0.17, 0.34] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003 Sia b] 2003 Song a] 2011 Song c] 2011 Song c] 2011 Vincent S 2005	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.0571	0.0577 0.0384 0.0387 0.038 0.0593 0.0665 0.0341 0.0626 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.0766 0.0411 0.0207 , df = 17	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 140 988	Total 59 60 49 50 49 64 47 56 46 46 49 49 55 55 40 40 40 40 40 140 988	4.5% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.4% 82.1%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.11 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10]	
3	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003 Song a] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song d] 2011 Vincent S 2005 Subtotal (95% CI) Heterogeneity: Tau ² =	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.0571	0.0577 0.0384 0.0387 0.038 0.0593 0.0665 0.0341 0.0626 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.0766 0.0411 0.0207 , df = 17	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 140 988	Total 59 60 49 50 49 64 47 56 46 46 49 49 55 55 40 40 40 40 40 140 988	4.5% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.4% 82.1%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.11 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10]	
5	1.2.1 ISB ± sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori a] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Sia b] 2003 Sia b] 2003 Song a] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Vincent S 2005 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	0.2542 0.0833 0.0612 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.0571 0.0571 0.01; Chi ² = 70.26 Z = 6.86 (P < 0.00	0.0577 0.0384 0.0387 0.038 0.0593 0.0665 0.0341 0.0626 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.0766 0.0411 0.0207 , df = 17	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 140 988	Total 59 60 49 50 49 64 47 56 46 46 49 49 55 55 40 40 40 40 40 140 988	4.5% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.4% 82.1%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.11 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10]	
3	1.2.1 ISB ± sedationChierichini a] 2015Chierichini b] 2015Hasanein a] 2014Hasanein b] 2014Hasanein c] 2014Kim b] 2015Liguori a] 1998Liguori b] 1998Liguori c] 1998Nallam a] 2015Nallam b] 2015Sia a] 2003Song a] 2011Song c] 2011Song c] 2011Song c] 2011Song d] 2011Vincent S 2005Subtotal (95% CI)Heterogeneity: Tau² =Test for overall effect:1.2.2 GA ± ISB	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.0571 0.0571 0.01; Chi ² = 70.26 Z = 6.86 (P < 0.00	0.0577 0.0384 0.0387 0.0593 0.0593 0.0655 0.0341 0.0665 0.0341 0.0626 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.0411 0.0207 , df = 17 001)	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 55 40 40 40 40 40 140 988 (P < 0.000	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 55 55 55 40 40 40 40 40 288 001); I ²	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.4% 82.1% = 76%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.22 [0.17, 0.41] 0.11 [0.02, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19]	
8	1.2.1 ISB \pm sedationChierichini a] 2015Chierichini b] 2015Hasanein a] 2014Hasanein c] 2014Hasanein c] 2014Hasanein c] 2014Kim b] 2015Liguori a] 1998Liguori c] 1998Liguori c] 1998Nallam a] 2015Nallam b] 2015Sia a] 2003Song a] 2011Song c] 2011Song c] 2011Song c] 2011Song c] 2011Subtotal (95% CI)Heterogeneity: Tau ² =Test for overall effect:1.2.2 GA \pm ISBJang a] 2016	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2705 0.35 0.057 0.057 0.0571 0.001; Chi ² = 70.26 Z = 6.86 (P < 0.00	0.0577 0.0384 0.0387 0.038 0.0593 0.0593 0.0665 0.0341 0.0665 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.0766 0.0766 0.0766 0.0766 0.0411 0.0207 , df = 17 001)	Total 59 60 49 50 49 64 47 56 46 49 49 49 55 55 55 40 40 40 40 140 988 (P < 0.000	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 55 50 40 40 40 40 40 140 988 001); I ²	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.4% 4.6% 82.1% 82.1% 82.2%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.11 [0.02, 0.20] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19] 0.48 [0.28, 0.68]	
3	1.2.1 ISB \pm sedationChierichini a] 2015Chierichini b] 2015Hasanein a] 2014Hasanein b] 2014Hasanein c] 2014Kim b] 2015Liguori a] 1998Liguori c] 1998Liguori c] 1998Nallam a] 2015Nallam b] 2015Sia b] 2003Song a] 2011Song c] 2011Song c] 2011Song d] 2011Vincent S 2005Subtotal (95% CI)Heterogeneity: Tau² =Test for overall effect:1.2.2 GA \pm ISBJang a] 2016Jansen a] 2014Jansen b] 2014	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.057 0.0571 0.01; Chi ² = 70.26 Z = 6.86 (P < 0.00	0.0577 0.0384 0.0387 0.038 0.0593 0.0575 0.0665 0.0341 0.0662 0.0612 0.0387 0.0446 0.0622 0.0517 0.0766 0.0776 0.07666 0.07666 0.07666 0.07666 0.07666 0.07666 0.07666 0.07666 0.	Total 59 60 49 50 49 64 47 56 46 47 56 40 49 49 55 55 40 40 40 40 40 25 88 (P < 0.000	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 140 988 001); I ² 25 25	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.4% 4.6% 4.7% 82.1% = 76%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19] 0.48 [0.28, 0.68] 1.00 [0.93, 1.07]	
3	1.2.1 ISB \pm sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori b] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Vincent S 2005 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.2.2 GA \pm ISB Jang a] 2016 Jansen a] 2014	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.275 0.35 0.057 0.0571 0.01; Chi ² = 70.26 Z = 6.86 (P < 0.00	0.0577 0.0384 0.0387 0.038 0.0593 0.0665 0.0341 0.0665 0.0341 0.0622 0.0517 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.07766 0.0766 0.0776 0.0766 0.0776 0.0766 0.0776 0.0101 0.0207	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 140 988 (P < 0.000 25 25 25 42	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 140 988 001); I ² 25 25 42	$\begin{array}{c} 4.5\% \\ 4.6\% \\ 4.6\% \\ 4.5\% \\ 4.5\% \\ 4.5\% \\ 4.5\% \\ 4.5\% \\ 4.5\% \\ 4.6\% \\ 4.6\% \\ 4.6\% \\ 4.6\% \\ 4.4\% \\ 4.6\% \\ 4.4\% \\ 4.6\% \\ 82.1\% \\ = 76\% \end{array}$	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19] 0.48 [0.28, 0.68] 1.00 [0.93, 1.07] 0.83 [0.72, 0.95]	
5	1.2.1 ISB \pm sedationChierichini a] 2015Chierichini b] 2015Hasanein a] 2014Hasanein b] 2014Hasanein c] 2014Kim b] 2015Liguori a] 1998Liguori c] 1998Liguori c] 1998Nallam a] 2015Nallam b] 2015Sia b] 2003Song a] 2011Song c] 2011Song c] 2011Song d] 2011Vincent S 2005Subtotal (95% CI)Heterogeneity: Tau² =Test for overall effect:1.2.2 GA \pm ISBJang a] 2016Jansen a] 2014Jansen b] 2014	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.2909 0.1 0.275 0.35 0.0571 0.05771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710000000000	0.0577 0.0384 0.0387 0.038 0.0593 0.0573 0.0665 0.0341 0.0626 0.0612 0.0347 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.0776 0.0766 0.0776 0.0766 0.0411 0.0207 0.0101 0.1016 0.0381 0.0381 0.0381 0.0547 0.0547 0.0547	Total 59 60 49 50 49 64 47 56 46 46 49 49 49 55 55 55 40 40 40 40 40 40 25 55 55 40 40 40 40 140 988 (P < 0.000	Total 59 60 49 50 49 64 47 56 46 46 49 95 55 55 40 40 40 40 40 988 001); I ² 25 25 25 25 25 242 41 133	4.5% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.6% 4.6% 4.7% 82.1% = 76%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19] 0.48 [0.28, 0.68] 1.00 [0.93, 1.07] 0.83 [0.72, 0.95] 0.88 [0.77, 0.99]	
3	1.2.1 ISB \pm sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori a] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2014 Jansen b] 2016 Jansen c] 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	0.2542 0.0833 0.0612 0.06 0.2041 0.2813 0.2766 0.0536 0.2174 0.2245 0.0612 0.1091 0.2909 0.1 0.2909 0.1 0.275 0.35 0.0571 0.05771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.07771 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710 0.077710000000000	0.0577 0.0384 0.0387 0.038 0.0593 0.0573 0.0665 0.0341 0.0626 0.0612 0.0347 0.0446 0.0622 0.0517 0.0766 0.0766 0.0766 0.0776 0.0766 0.0776 0.0766 0.0411 0.0207 0.0101 0.1016 0.0381 0.0381 0.0381 0.0547 0.0547 0.0547	Total 59 60 49 50 49 64 47 56 46 49 49 49 55 55 40 40 40 40 40 140 988 (P < 0.000 25 25 25 42 41 133 2 < 0.000	Total 59 60 49 50 49 50 49 56 46 49 55 50 40 40 40 988 001); I ² 25 42 41 133 1); I ² = 8	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.6% 4.6% 4.6% 4.6	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19] 0.48 [0.28, 0.68] 1.00 [0.93, 1.07] 0.83 [0.72, 0.95] 0.88 [0.77, 0.99] 0.82 [0.65, 0.98]	
3	1.2.1 ISB \pm sedationChierichini a] 2015Chierichini b] 2015Hasanein a] 2014Hasanein c] 2014Hasanein c] 2014Hasanein c] 2014Hasanein c] 2014Liguori a] 1998Liguori b] 1998Liguori c] 1998Nallam a] 2015Nallam b] 2015Sia a] 2003Song a] 2011Song c] 2016Jansen a] 2016Jansen a] 2016Jansen a] 2014Subtotal (95% CI)Heterogeneity: Tau² =Test for overall effect:Total (95% CI)	$\begin{array}{c} 0.2542\\ 0.0833\\ 0.0612\\ 0.06\\ 0.2041\\ 0.2813\\ 0.2766\\ 0.0536\\ 0.2174\\ 0.2245\\ 0.0612\\ 0.1091\\ 0.2909\\ 0.1\\ 0.275\\ 0.35\\ 0.05\\ 0.0571\\ 0.01; \ Chi^2 = 70.26\\ Z = 6.86\ (P < 0.00\\ 0.48\\ 1\\ 0.8333\\ 0.878\\ 0.02; \ Chi^2 = 25.37\\ Z = 9.67\ (P < 0.00\\$	0.0577 0.0384 0.0387 0.038 0.0593 0.0655 0.0341 0.0665 0.0341 0.0665 0.0387 0.0446 0.0622 0.0517 0.0766 0.0767 0.0777 0.0777 0.0777 0.0777 0.0776 0.0777 0.0777 0.0777 0.0776 0.0777 0.0777 0.0776 0.0777 0.0777 0.0777 0.0777 0.0776 0.07770 0.07770 0.07770 0.07770 0.07770 0.07770 0.077700 0.077700000000	Total 59 60 49 50 49 64 47 56 46 49 49 49 55 55 40 40 40 40 40 40 140 988 (P < 0.000 25 25 42 25 42 41 133 2 < 0.000 25 25 42 41 133 2 < 0.000	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 40 40 40 140 988 001); I ² 25 25 42 41 133 1); I ² = 8 1121	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.7% 82.1% = 76% 4.2% 4.6% 4.6% 17.9% 38%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19] 0.48 [0.28, 0.68] 1.00 [0.93, 1.07] 0.83 [0.72, 0.95] 0.88 [0.77, 0.99]	IV, Random, 95% Cl
3	1.2.1 ISB \pm sedation Chierichini a] 2015 Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Liguori a] 1998 Liguori a] 1998 Liguori c] 1998 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2014 Jansen b] 2016 Jansen c] 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	$\begin{array}{c} 0.2542\\ 0.0833\\ 0.0612\\ 0.06\\ 0.2041\\ 0.2813\\ 0.2766\\ 0.0536\\ 0.2174\\ 0.2245\\ 0.0612\\ 0.1091\\ 0.275\\ 0.35\\ 0.0571\\ 0.071\\ 0.275\\ 0.35\\ 0.0571\\ 0.071\\ 0.275\\ 0.35\\ 0.0571\\ 0.01; \ Chi^2 = 70.26\\ Z = 6.86\ (P < 0.00\\ 0.48\\ 1\\ 0.8333\\ 0.878\\ 0.02; \ Chi^2 = 25.37\\ Z = 9.67\ (P < 0.00\\ 0.08; \ Chi^2 = 859.12\\ 0.08; \ Chi^2 = 859.12\\ 0.0833 \\ 0.003; \ Chi^2 = 859.12\\ 0.008; \ Chi^2 = 859.12\\$	0.0577 0.0384 0.0387 0.038 0.0593 0.0665 0.0341 0.0665 0.0341 0.0662 0.0387 0.0466 0.0612 0.0387 0.0766 0.077 0.0766 0.077 0.0766 0.077 0.0766 0.077 0.0766 0.0766 0.077 0.0766 0.077 0.0766 0.0776 0.0766 0.0766 0.0776 0.0766 0.0776 0.0766 0.0776 0.0766 0.0776 0.0766 0.0776 0.0766 0.0776 0.0766 0.0776 0.0776 0.0766 0.0777 0.0766 0.0777 0.0766 0.0777 0.0776 0.0777 0.0776 0.0777 0.0776 0.0777 0.0777 0.0776 0.0777 0.0777 0.0777 0.0776 0.0777 0.0777 0.0777 0.0776 0.0777 0.0777 0.0777 0.0777 0.0776 0.0777 0.0777 0.0777 0.0776 0.07770 0.07770 0.07770 0.07770 0.07770 0.07770 0.077700 0.077700 0.077700000000	Total 59 60 49 50 49 64 47 56 46 49 49 49 55 55 40 40 40 40 40 40 140 988 (P < 0.000 25 25 42 25 42 41 133 2 < 0.000 25 25 42 41 133 2 < 0.000	Total 59 60 49 50 49 64 47 56 46 49 49 55 55 40 40 40 40 40 40 40 40 140 988 001); I ² 25 25 42 41 133 1); I ² = 8 1121	4.5% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.6% 4.6% 4.6% 4.6% 4.4% 4.6% 4.7% 82.1% = 76% 4.2% 4.6% 4.6% 17.9% 38%	IV, Random, 95% Cl 0.25 [0.14, 0.37] 0.08 [0.01, 0.16] 0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.28 [0.15, 0.41] 0.05 [-0.01, 0.12] 0.22 [0.09, 0.34] 0.22 [0.10, 0.34] 0.22 [0.10, 0.34] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.29 [0.17, 0.41] 0.10 [-0.00, 0.20] 0.28 [0.12, 0.43] 0.35 [0.20, 0.50] 0.05 [-0.03, 0.13] 0.06 [0.02, 0.10] 0.15 [0.11, 0.19] 0.48 [0.28, 0.68] 1.00 [0.93, 1.07] 0.83 [0.72, 0.95] 0.88 [0.77, 0.99] 0.82 [0.65, 0.98]	IV, Random, 95% Cl

Figure 1: Bradycardia (A) and HBE (B) meta-analysis forest plots. All hypotension incidences were included. BCP – Beach chair position; Cl-Confidence interval; GA – General anaesthesia; HBE - Hypotension-bradycardia episode; ISB – Interscalene block; IV- Inverse variance; SE -Standard error

	Epinephi		Cont				Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Tota	Weig	ght M-	H, Random, 95% Cl	M-H, Random, 95% Cl
Chierichini 2015	15	59	5	60	47.	2%	3.75 [1.26, 11.12]	
Sia 2003	16	55	6	55	52.	8%	3.35 [1.20, 9.37]	
Total (95% CI)		114		115	100.	0%	3.53 [1.67, 7.46]	•
Total events	31		11					
Heterogeneity: Tau ² =	0.00; Chi ² =	0.02,	df = 1 (F	= 0.88	5); ² = (0%	F	01 0.1 1 10 1
Test for overall effect: 2	Z = 3.31 (P	= 0.00	(900				0.	01 0.1 1 10 1 Epinephrine Control
								Epinepinine Control
			5	ipine	BCD		Risk Difference	Risk Difference
Study or Subgroup	Risk Differe	ance	SE			Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.1.1 Epinephrine used		nce	52	Total	Total	weight	14, Random, 55% CI	
Chierichini a] 2015		2542 (0577	59	59	5.0%	0.25 [0.14, 0.37]	
Liguori a] 1998		2766 (47	47	4.4%	0.28 [0.15, 0.41]	
Liguori b] 1998)536 (56	56	6.7%	0.05 [-0.01, 0.12]	-
Liguori c] 1998		2174 (46	46	4.7%	0.22 [0.09, 0.34]	
Sia b] 2003		2909 (55	55	4.7%	0.29 [0.17, 0.41]	
Vincent S 2005		0571 (140	140	7.6%	0.06 [0.02, 0.10]	-
Subtotal (95% CI)	0.0			403	403	33.1%	0.18 [0.09, 0.27]	•
Heterogeneity: Tau ² = 0. Test for overall effect: Z				0.0000	1), 1	03%		
Test for overall effect: Z 2.1.2 Without epinephr	= 3.86 (P =	0.0001)					
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015	= 3.86 (P = rine 0.0	0.0001) 0.0384	60	60	6.4%	0.08 [0.01, 0.16]	-
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014	= 3.86 (P = rine 0.0 0.0	0.0001 0833 (0612 () 0.0384 0.0387	60 49	60 49	6.4% 6.4%	0.06 [-0.01, 0.14]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014	= 3.86 (P = rine 0.0 0.0	0.0001 0833 (0 0612 (0 0.06) 0.0384 0.0387 0.038	60 49 50	60 49 50	6.4% 6.4% 6.4%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014	= 3.86 (P = rine 0.0 0.0 0.2	0.0001 0833 (0 0612 (0 0.06 2041 (0) 0.0384 0.0387 0.038 0.0593	60 49 50 49	60 49 50 49	6.4% 6.4% 6.4% 4.9%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015	= 3.86 (P = rine 0.0 0.2 0.2	0.0001 0833 (0 0612 (0 0.06 2041 (0 2813) 0.0384 0.0387 0.038 0.0593 0.057	60 49 50 49 64	60 49 50 49 64	6.4% 6.4% 6.4% 4.9% 5.0%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015	= 3.86 (P = rine 0.0 0.2 0.2 0.2	0.0001 0833 (0 0612 (0 0.06 2041 (0 2813 2245 (0) 0.0384 0.0387 0.038 0.0593 0.057 0.0612	60 49 50 49 64 49	60 49 50 49 64 49	6.4% 6.4% 6.4% 5.0% 4.8%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2	0.0001 0833 (0 0612 (0 0.06 2041 (0 2813 2245 (0 0612 (0) 0.0384 0.0387 0.038 0.0593 0.057 0.0612 0.0387	60 49 50 49 64 49 49	60 49 50 49 64 49 49	6.4% 6.4% 4.9% 5.0% 4.8% 6.4%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2	0.0001 0833 (0 0612 (0 0.06 2041 (0 2813 2245 (0 0612 (0 1091 (0) 0.0384 0.0387 0.038 0.0593 0.057 0.0612 0.0387 0.0387 0.0446	60 49 50 64 49 49 55	60 49 50 49 64 49 49 55	6.4% 6.4% 4.9% 5.0% 4.8% 6.4% 5.9%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2 0.2	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (1091 (0.1 () 0.0384 0.0387 0.038 0.0593 0.057 0.0612 0.0387 0.0446 0.0517	60 49 50 49 64 49 55 40	60 49 50 49 64 49 49 55 40	6.4% 6.4% 4.9% 5.0% 4.8% 6.4% 5.9% 5.4%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song b] 2011	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2 0.2 0.2	0.0001 0833 (0 0612 (0 0.06 2041 (0 2813 2245 (0 0612 (0 1091 (0) 0.0384 0.0387 0.038 0.0593 0.057 0.0612 0.0387 0.0446 0.0517 0.0596	60 49 50 64 49 49 55	60 49 50 49 64 49 49 55	6.4% 6.4% 4.9% 5.0% 4.8% 6.4% 5.9%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20] 0.15 [0.03, 0.27]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.1	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (1091 (0.1 (0.15 () 0.0384 0.0387 0.038 0.0593 0.0612 0.0387 0.0387 0.0387 0.0446 0.0517 0.0596 0.0722	60 49 50 49 64 49 55 40 40	60 49 50 49 64 49 64 49 55 40 40	6.4% 6.4% 6.4% 5.0% 4.8% 6.4% 5.9% 5.4% 4.9%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam a] 2015 Sia a] 2003 Song a] 2011 Song b] 2011 Song c] 2011	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.1	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (0612 (0.15 (.275 () 0.0384 0.0387 0.038 0.0593 0.0612 0.0387 0.0387 0.0387 0.0446 0.0517 0.0596 0.0722	60 49 50 49 64 49 55 40 40	60 49 50 49 64 49 49 55 40 40	6.4% 6.4% 4.9% 5.0% 6.4% 5.9% 5.4% 4.9% 4.1%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20] 0.15 [0.03, 0.27] 0.28 [0.13, 0.42]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2011 Song c] 2011	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.1	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (0.1 (0.1 (0.15 (0.275 (0.05 () 0.0384 0.0387 0.038 0.0593 0.0612 0.0612 0.0387 0.0446 0.0446 0.04517 0.0596 0.0722 0.0411	60 49 50 49 64 49 55 40 40 40 40 585	60 49 50 49 64 49 49 55 40 40 40 40 585	6.4% 6.4% 4.9% 5.0% 4.8% 5.9% 5.4% 4.9% 4.1% 6.2% 66.9%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20] 0.15 [0.03, 0.27] 0.28 [0.13, 0.42] 0.05 [-0.03, 0.13]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein b] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2011 Song c] 2011 Song d] 2011 Subtotal (95% CI)	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2 0.1 0 0 0.1 0 0.1 0 0.1 0 0.1 0 0.1 0.1	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (0.15 (0.15 (0.15 (0.275 (0.05 (8.28, d) 0.0384 0.0387 0.038 0.0593 0.0572 0.0446 0.0517 0.0517 0.0596 0.0722 0.0411 ff = 11 (P	60 49 50 49 64 49 55 40 40 40 40 585	60 49 50 49 64 49 49 55 40 40 40 40 585	6.4% 6.4% 4.9% 5.0% 4.8% 5.9% 5.4% 4.9% 4.1% 6.2% 66.9%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20] 0.15 [0.03, 0.27] 0.28 [0.13, 0.42] 0.05 [-0.03, 0.13]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2012 Song c] 2013 Song c] 201	= 3.86 (P = rine 0.0 0.2 0.2 0.2 0.2 0.2 0.1 0 0 0.1 0 0.1 0 0.1 0 0.1 0 0.1 0.1	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (0.15 (0.15 (0.15 (0.275 (0.05 (8.28, d) 0.0384 0.0387 0.038 0.0593 0.0572 0.0446 0.0517 0.0517 0.0596 0.0722 0.0411 ff = 11 (P	60 49 50 49 64 49 55 40 40 40 40 585	60 49 50 49 64 49 55 40 40 40 585); l ² = 6	6.4% 6.4% 4.9% 5.0% 4.8% 5.9% 5.4% 4.9% 4.1% 6.2% 66.9%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20] 0.15 [0.03, 0.27] 0.28 [0.13, 0.42] 0.05 [-0.03, 0.13]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam b] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z	= 3.86 (P = ine 0.0 0.2 0.2 0.2 0.2 0.2 0.2 0.2	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (0.15 (0.15 (0.05 (8.28, d 0.0000) 0.0384 0.0387 0.038 0.0593 0.057 0.0612 0.0387 0.0446 0.0517 0.0596 0.0722 0.0411 If = 11 (P	60 49 50 49 64 49 55 40 40 40 585 = 0.003	60 49 50 49 64 49 55 40 40 40 585); l ² = 6 988	6.4% 6.4% 4.9% 5.0% 4.8% 6.4% 5.9% 5.4% 4.1% 6.2% 66.9% 1%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20] 0.15 [0.03, 0.27] 0.28 [0.13, 0.42] 0.05 [-0.03, 0.13] 0.13 [0.08, 0.17] 0.14 [0.10, 0.18]	
Test for overall effect: Z 2.1.2 Without epinephr Chierichini b] 2015 Hasanein a] 2014 Hasanein c] 2014 Hasanein c] 2014 Kim b] 2015 Nallam a] 2015 Nallam a] 2015 Nallam b] 2015 Sia a] 2003 Song a] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Song c] 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z	= 3.86 (P = ine 0.0 0.2 0.2 0.2 0.2 0.2 0.2 0.2	0.0001 0833 (0612 (0.06 2041 (2813 2245 (0612 (0.15 (0.15 (0.05 (8.28, d 0.0000 1.43, d) 0.0384 0.0387 0.038 0.0593 0.057 0.0612 0.0387 0.0446 0.0517 0.0446 0.0576 0.0722 0.0411 If = 11 (P I1) If = 17 (P	60 49 50 49 64 49 55 40 40 40 585 = 0.003	60 49 50 49 64 49 55 40 40 40 585); l ² = 6 988	6.4% 6.4% 4.9% 5.0% 4.8% 6.4% 5.9% 5.4% 4.1% 6.2% 66.9% 1%	0.06 [-0.01, 0.14] 0.06 [-0.01, 0.13] 0.20 [0.09, 0.32] 0.28 [0.17, 0.39] 0.22 [0.10, 0.34] 0.06 [-0.01, 0.14] 0.11 [0.02, 0.20] 0.10 [-0.00, 0.20] 0.15 [0.03, 0.27] 0.28 [0.13, 0.42] 0.05 [-0.03, 0.13] 0.13 [0.08, 0.17]	-0.5 0 0.5 1

Figure 2: Effect of β-agonists (epinephrine) on bradycardia/HBEs. A. Forest plot for the use of epinephrine. B. Subgroup analysis forest plots for sub-groups using epinephrine and for those without. GA subjects are not included in this analysis. BCP - Beach chair position; CI - Confidence interval; GA – General anaesthesia; HBE - Hypotension-bradycardia episode; IV - Inverse variance. M-H - Mantel-Haenszel

Relationship between rSO₂ SjvO₂ and HR

Seventeen SGs^[33-35,46,56,60,65] evaluated the HR and rSO₂ 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 rSO₂ values (r = 0.608, 95%CI, 0.439 to 0.735, P < 0.001). Correlation was attempted between HR and SjvO₂ absolute values from 12SGs.^[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 SjvO₂ values [Figure 5].

Use of PVIs and effect on HR, rSO_2 and HR- rSO_2 relationships,^[15,33-35] details of physiological controls,^[31,53,59,62] vaso-active drugs consumption^[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

C	Fentanyl	used	Con	trol		1	Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	s Total	Weigh	<u>t M-H</u> ,	, Random, 95% Cl	M-H, Random, 95% Cl
Song a] 2011	8	80	() 40	50.0%	6 8	.60 [0.51, 145.42]	
Song b] 2011	8	80			50.0%		.60 [0.51, 145.42]	
Total (95% CI)		160		80	100.0%	6 8	8.60 [1.17, 63.53]	
Total events	16		c		,			
Heterogeneity: Tau ² =		- 0 00 /			$1^2 = 0\%$		L	
Test for overall effect:				- 1.00),	1 - 078		0.00	1 0.1 1 10 1000 Fentanyl Control
1			5	Supine	ВСР		Risk Difference	Risk Difference
Study or Subgroup	Risk Diffe	erence	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.4.1 Fentanyl used								
Hasanein a] 2014	(0.0612	0.0387	49	49	8.2%	0.06 [-0.01, 0.14]	
Hasanein b] 2014			0.038	50	50	8.2%	0.06 [-0.01, 0.13]	+ - -
Hasanein c] 2014	(0.2045		49	49	6.3%	0.20 [0.09, 0.32]	
Nallam a] 2015		0.2245		49	49	6.1%	0.22 [0.10, 0.34]	
Nallam b] 2015		0.0612		49	49	8.2%	0.06 [-0.01, 0.14]	+ - -
Song b]2011	,	0.275		40	40	5.3%	0.28 [0.13, 0.42]	
Song c] 2011			0.0722	40	40	5.0%	0.35 [0.20, 0.50]	
Subtotal (95% CI)		0.55	0.0700	326	326	5.0% 47.2%	0.35 [0.20, 0.50]	
	0.01.01:2	25 60					0.10 [0.00, 0.24]	•
Heterogeneity: Tau ² = Test for overall effect:				- 0.0003	o), i- = 77	/0		
2.4.2 Fentanyl not us	ed							
Chierichini a] 2015	(0.2542	0.0577	59	59	6.4%	0.25 [0.14, 0.37]	
Chierichini b] 2015	(0.0833	0.0384	60	60	8.2%	0.08 [0.01, 0.16]	
Sia a] 2003	(0.1095	0.0446	55	55	7.6%	0.11 [0.02, 0.20]	
Sia b] 2003	(0.2909	0.0622	55	55	6.0%	0.29 [0.17, 0.41]	
Song a] 2011		0.1	0.0517	40	40	7.0%	0.10 [-0.00, 0.20]	
Song d] 2011		0.05	0.0411	40	40	7.9%	0.05 [-0.03, 0.13]	+- -
Vincent S 2005	(0.0571	0.0207	140	140	9.7%	0.06 [0.02, 0.10]	-
Subtotal (95% CI)				449	449	52.8%	0.12 [0.06, 0.18]	•
Heterogeneity: Tau ² = Test for overall effect:				= 0.001)	; l² = 73%	6		
Total (95% CI)				775	775	100.0%	0.14 [0.09, 0.18]	•
Heterogeneity: Tau ² =	0 01. Chi ² =	49 41	df = 13 (F					· · / · / · / · / · / · / · / · / · / · _ / / · _ / / · _ / / · _ / / / /
Test for overall effect:				0.000	,01),1	1470	-1	
Test for subgroup diffe				P = 0.45)	, l² = 0%			Supine BCP
study or Subgroup	with β-block Events	kers Total	without f Events		rs otal We		lds Ratio (Non-event) M-H, Random, 95% Cl	Odds Ratio (Non-event) M-H, Random, 95% Cl
iguori 1998	Events 3	56	23		93 100		5.80 [1.65, 20.36]	
0	1.0000 ()							—
otal (95% CI)	-	56			93 100	1.0%	5.80 [1.65, 20.36]	
otal events	3		23	3				
leterogeneity: Not appli							-	0.02 0.1 1 10 50
est for overall effect: Z	= 2.75 (P = (J.UO6)						without β -blockers with β -blockers
	Prophylactic	ondans	setron	No onda	nsetron		Odds Ratio (Non-event)	
Study or Subgroup	Events		Total	Events	Tota			
Hasanein a] 2014		3	49	10	49		the read file second second second	
Hasanein b] 2014		3	50	10	49			
Nallam 2015	3	3	49	11	49	33.7%	6 4.44 [1.15, 17.07]
Total (95% CI)			148		147	100.0%	4.13 [1.89, 9.02]	-
Total events	ç	Э		31				
Listene servite Tau? - 0	00: Chi ² = 0.0	02. df = 2	P = 0.99	$(); ^2 = 0\%$	5			0.05 0.2 1 5 20
Heterogeneity: Tau ² = 0.								0.05 0.2 1 5 20

Figure 3: Effect of drugs that can modify incidence of bradycardia/HBEs. Forest plots for fentanyl (C, D), β-blockers (E) and ondansetron (F) on bradycardia/HBEs. GA subjects are not included in this analysis. BCP - Beach chair position; CI - Confidence interval; GA – General anaesthesia; IV - Inverse variance. M-H - Mantel-Haenszel

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

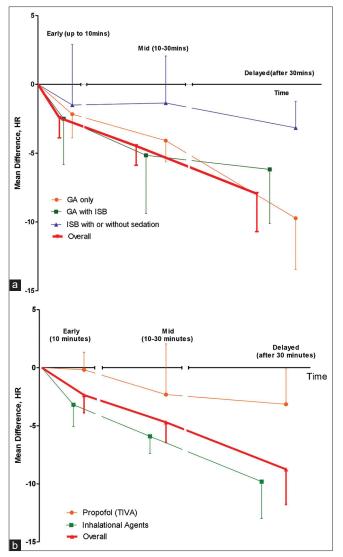


Figure 4: Fall of HR over time, for pooled serial measurements under anaesthesia. The mean differences (MDs) are studied for the first 10 minutes, 11-30 minutes and after 30 minutes of beach-chair position from pre-BCP levels. For different types of anaesthesia (a) and maintenance agents (b), the trends are shown. GA - General anaesthesia; ISB - Interscalene block; TIVA - Total intravenous anaesthesia

are few in number. 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

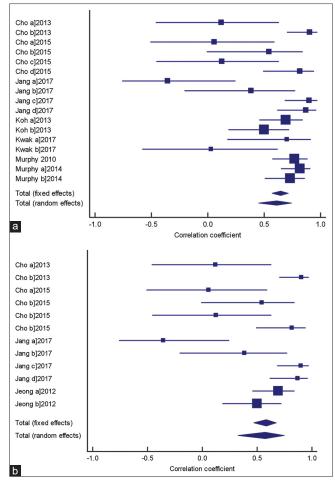


Figure 5: Meta-correlation-analysis depicting the relationship between rSO_2 (a), SjvO₂ (b) and HR. 95% confidence intervals are shown. HR - Heart rate; rSO_2 - Regional cerebral oxygen saturation; SjvO₂ - Jugular venous oxygen saturation

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

			Table 2: Sensitivity analysi				
Factor/Covariate	Time	Number of subjects	Mean difference, HR (95% confidence interval)	ľ	<i>P</i> * for χ ² heterogeneity	P, overall effect	Number of
Use of PVIs		107	· · · · · · · · · · · · · · · · · · ·	0.20/	<0.00001	0.23	study groups
Use of PVIS	Early		3.67 (-2.4, 9.7)	83%			7
	Mid	58	-0.81 (-4.39, 2.78)	0%	0.94	0.66	3
Inducing agent, Propofol	Early	1333	2.72 (1.21, 4.23)	79%	<0.00001	0.0005	46
Inducing agent, Thiopentone	Early	120	2.18 (-0.95, 5.3)	0%	0.98	0.17	5
Remifentanil	Early	811	2.16 (0.35, 3.96)	79%	<0.00001	0.02	27
	Mid	444	5.62 (1.99, 9.25)	83%	<0.00001	0.002	18
	Delayed	229	8.8 (5.41, 12.18)	50%	0.05	<0.00001	8
Fentanyl	Early	111	6.02 (2.28,9.76)	78%	<0.00001	0.002	11
	Mid	296	6.98 (4.95,9.01)	0%	0.74	<0.00001	11
	Delayed	110	16.61 (13.01,20.21)	61%	0.03	<0.00001	5
Alfentanil	Early	80	4.59 (-1.03,10.22)	61%	0.05	0.11	4
	Mid	80	3.13 (-0.45,6.70)	0%	0.66	0.09	4
	Delayed	40	2.93 (-1.53,7.39)	0%	0.63	0.2	2
Sufentanil	Early	53	-0.8 (-5.41, 3.81)	NA	NA	0.73	1
	Mid	117	0.63 (-1.96,3.21)	0%	0.61	0.63	4
TIVA, propofol	Early	480	0.59 (-0.93,2.10)	0%	0.88	0.45	13
	Mid	340	2.72 (-1.64,7.07)	85%	<0.00001	0.22	15
	Delayed	100	3.55 (0.46,6.64)	0%	0.86	0.02	3
Sevoflurane	Early	826	3.55 (1.56, 5.53)	84%	<0.00001	0.0005	33
	Mid	736	5.84 (4.23, 7.45)	39%	0.02	<0.00001	27
	Delayed	420	9.54 (5.9, 13.2)	83%	<0.00001	<0.00001	16
Desflurane	Early	87	2.04 (-1.18, 5.25)	0%	0.89	0.21	4
	Mid	106	7.32 (3.64, 10.99)	40%	0.16	<0.0001	5
	Delayed	60	13.3 (9.72, 16.88)	0%	0.5	<0.00001	3
Randomised trials	Early	1072	2.41 (0.69, 4.14)	80%	<0.00001	0.006	41
	Mid	649	4.33 (2.81, 5.84)	27%	0.08	<0.00001	32
	Delayed	530	9.35 (6.09, 12.61)	82%	<0.0001	<0.00001	20
Study Controls	Early	709	1.73 (0.03, 3.43)	32%	0.07	0.05	23
	Mid	776	6.09 (3.54, 8.65)	75%	<0.0001	<0.0001	26
	Delayed	361	8.84 (5.78, 11.89)	61%	0.003	<0.00001	12

PVI – Prophylactic vasopressor infusion; TIVA – Total intravenous anaesthesia; HR – Heart rate; χ^2 -Chi-square; *critical *P*=0.05; significant *P* are bold and italicised

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.^[6] 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.^[8,12] 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.^[12] 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-rSO₂ 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_2 at the medullary vasomotor centre (VMC) is un-monitored. We have demonstrated a HR-rSO₂/SjvO₂ association through meta-correlation analysis. There is a

dearth of literature on monitoring rSO₂ 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] 3.3%^[56] or lower absolute values of rSO₂.^[68] 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.^[69]

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.

Acknowledgements

We sincerely acknowledge Dr Rajani Kadri, M.S., Associate Professor, Department of Opthalmology, A J I M S & Research Centre, Mangalore for her excellent support, contribution and cooperation during the preparation of manuscript. We also thank Mr. Naveen Mishra, Pranavi and Poorvi for their kind help during manuscript preperation.

Financial support and sponsorship

Grants, sponsors, and funding sources that provided direct financial support to the research work contained in the manuscript: None declared for all above mentioned authors.

Conflicts of interest

There are no conflicts of interest.

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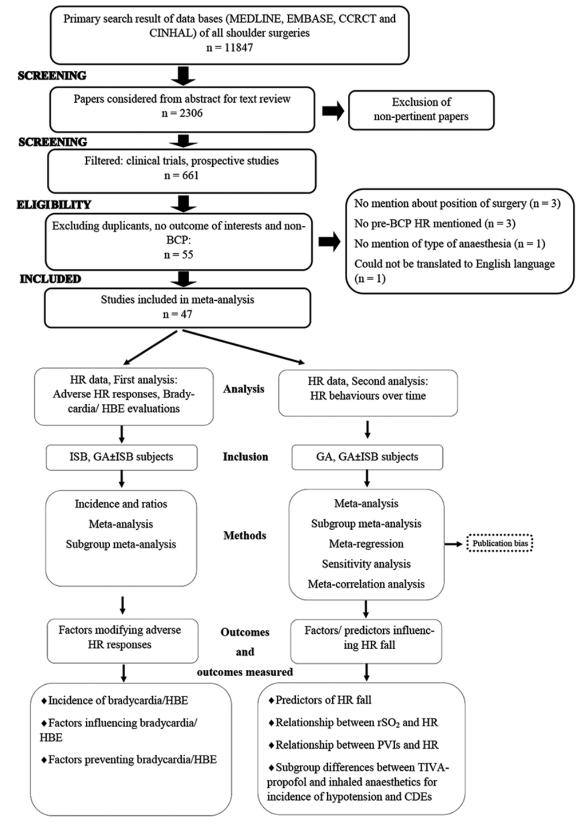
- 1. Beach chair position
- 2. Beach-chair position
- 3. BCP
- 4. BCP complication
- 5. BCP complications
- 6. BCP anaesthesia
- 7. BCP anesthesia
- Beach chair seated positioning
- 9. Beach chair seated anaesthesia
- 10. Beach chair seated surgery
- 11. OR/1 to 10 (3235)
- 12. Shoulder arthroscopy
- 13. Shoulder arthroplasty
- Shoulder arthroscopic surgery
- 15. Shoulder surgery
- 16. Shoulder scopy
- 17. OR/12 to 16 (37477)
- 18. Hemodynamic
- 19. Hemodynamic monitoring
- 20. Hemodynamic/clinical
- 21. Hemodynamic/anaesthetic
- 22. Hemodynamic
- 23. Haemodynamic monitoring
- 24. OR/18 to 23 (724087)
- 25. Heart rate
- 26. Heart rate response
- 27. Heart rate responses
- 28. Adverse hemodynamic events
- 29. Adverse heart rate response
- 30. OR/25 to 29 (338011)
- 31. Hypotensive bradycardic episode
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- 35. Hypotensive bradycardic
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- 37. OR/31 to 36 (37)
- 38. Bezold jarish reflex
- 39. Bezold jarish reflex activation
- Bezold jarisch like bradycardia reflex
- 41. Bezold jarish
- 42. Bezold jarisch like bradycardia reflex
- Bezold jarisch reflex like reaction
- 44. Bezold jarisch effects
- 45. Bezold jarisch like
- Bezold jarisch like bradycardia reflex
- 47. Bezold jarisch like effect
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- 49. Bezold jarisch like reflex
- 50. Bezold jarisch model
- 51. Bezold jarisch reflex
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- 53. Bezold jarisch reflex assay
- 54. Bezold jarisch reflex function
- 55. Bezold jarisch reflex induced decrease
- 56. Bezold jarisch reflex responses
- 57. Bezold jarisch reflex test

- 58. Bezold jarisch reflexes
- 59. Bezold jarisch response
- 60. Bezold jarisch s
- 61. OR/38 to 53 (377)
- 62. Bradycardia
- 63. Bradycardia/arrest
- 64. Bradycardia/asystole
- 65. Bradycardia/asystolia
- 66. Bradycardia/asystolic
- 67. Bradycardia/atrioventricular
- 68. Bradycardia/bradyarrhythmia
- 69. Bradycardia/cardiac
- 70. Bradycardia/case
- 71. Bradycardia/complications
- 72. Bradycardia/collapse
- 73. Bradycardia/desaturation
- 74. Bradycardia/hypotension
- 75. Bradycardia/sinus
- 76. Bradycardia/sinus arrest
- 77. Bradycardia/slow
- 78. Bradycardia/surgery
- 79. Bradycardia event
- 80. Bradycardia events
- 81. OR/62 to 80 (25618)
- 82. Epinephrine
- 83. Adrenaline
- 84. Beta blocker
- 85. Ondansetron
- 86. 11 OR 17 OR 24 OR 30 OR 37 OR 61 OR 81 (909292)
- 87. 17 AND 37 AND 61 (2289)
- 88. 11 AND 17 (214)
- 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)

IDENTIFICATION



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; rSO₂ - Regional cerebral oxygen saturation; TIVA - Total intravenous anaesthesia

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1 1		15ml 0.1% buyészcine, 15ml 2% lipnocine 3.9% leodeminezine, 10ten 26ml + E. Stun	2.9% keeloppiraciae, 10% ag 28 ml + E, Shg + Demedetanidae, 1	13-13ted of reprinceine, 0.75%	13-13bull of reprincting, 0.29%				. 9	2	2	80	3.9% sopractine, 2mg detanofilostidine	0.0% sopractine, 2mg detanolitonidine	8	8	0.03% superactive, 15-20ml	ALTH DIGRAMM	our requestions	2.12% superactive, 10ml	3.75% reprincisie, 5nd and decordeonidine 100%g		80	2		NE 15. continuous Abril		72	80	20	2	2	2	80	2	2	80	1% mephaceine, 20nd, 0.79% sopiraceine, 20nd	2	Represente	Bapriacence				1 90		0.17% supinomie, 10-20ml	9		1.774 Suppression, 19 mg/g, C, 1.20000	1.9% mopheniae, 18 mg/g, E, 1.20000	DN .		2.0% Hociversine. Med	and the second se	2	20	20	2		1.9% leveloppingenesies, 35ml	0.0% Arrodomycrocane, 50ad	. 9	0.2.9% levelopinscaine, alted	3.2.%6 bupiraceine, 40ml		0.5% speciation, 20ml	0.9% symbolization, 20mB	22	2	0.0% bage/scame, 2% idocate; 3%al	0.0% bigroscine, 2% blocine, 1.20000 adrendine, 5%til	a 1956 meriatrian landte	2.1% provincember 33.5%	3.17% reprincing 30-35%	3.7% bapitacine, 1% lidocaine or moyvacine, 41 ml	0.79% bupitacoine, 1% lidectine or mephacoine, 40 ml	0.15% bipitacine, 1% lidecane or nepriscine, 40 ml	0.19% bippiraciale. Ph lidocalae or mepiveciale. 40 ml	2	0.12% repracting. 30ml	2.0% http://www.action.com
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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 infra-red 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; TCl - 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 minute 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

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, rSO₂ and HR-rSO₂ 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 rSO₂ 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-rSO₂ 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, $I^2 = 72.5\%$, n = 90 and without PVIs use, r = 0.560, 95%CI, 0.332 to 0.727, P < 0.001, random effects, $I^2 = 80.81\%$, n = 291).

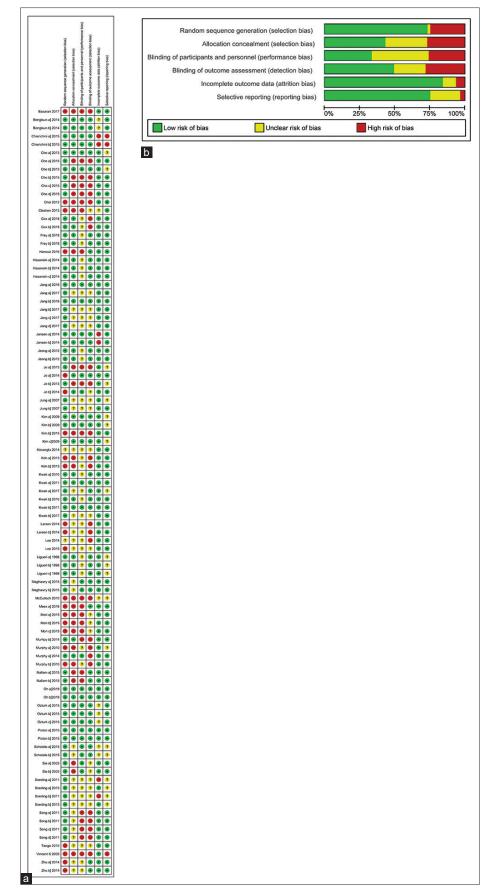
Relationship between rSO₂ and MBP: Twenty SGs^[16,33-35,46,56,60,65] evaluated MBP and rSO₂ at specific intervals over the entire BCP period. Data were recorded as statistical averages for absolute values of consecutive timings. Meta-correlation analysis showed statistically significant correlation between MBP and rSO₂ values (r = 0.597, 95% CI, 0.432 to 0.723, P < 0.001, random effects, $I^2 = 79.9\%$) 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 \pm ISB (n = 83) subjects^[54,56] than GA alone^[16,33,35,40,44,48,60,62] (n = 390) to maintain the desired BP (23.1 \pm 32.1 vs 15.4 \pm 27.3, per subject, respectively, P = 0.026). Ephedrine consumptions in inhalation anaesthesia^[16,35,40,44,48,54,56,60] (n = 396) and TIVA-propofol^[16,33,35] (n = 77) were 17.8 \pm 31.1 and 12.4 \pm 5.9 respectively (P = 0.236). CDEs, rSO₂ 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; rSO2 - regional cerebral oxygen saturation; SG - Study group; TIVA - Total intravenous anaesthesia.



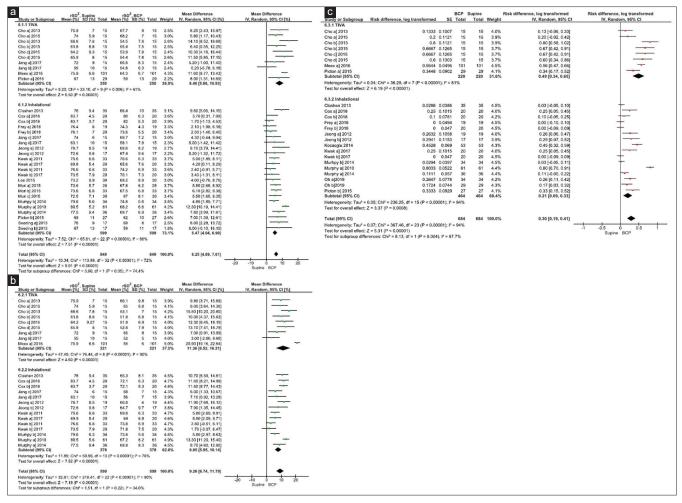
Supplementary Digital Content File 4: Risk of bias summary (a) and graph (b)

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	$I^2 = 70\%, P < 0.00001$	$I^2 = 43\%, P < 0.002$
3	Test for subgroup differences CDEs (Incidences, log-number of subjects)	<i>P</i> = 0.15	<i>P</i> < 0.0001
	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	<i>P</i> = 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	<i>P</i> = 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

Study or Subgroup		BCP :	Supine		og, Risk Difference	Log, Risk Differ	b BCP Suplone Risk difference, log transformed Risk difference, log transformed
	log[Log, Risk Difference] 5	E Total	Total		IV, Random, 95% Cl	IV, Random, 95	Study or Subgroup Risk difference, log transformed SE Total Total Weight IV, Random, 95% CI IV, Random, 95% CI
1.1 GA alone							5.2.1 TIVA
to a) 2013	-0.6667 0.12		15	1.3%	0.51 [0.40, 0.66]		Cho a] 2013 -0.6967 0.1265 15 15 2.3% -0.67 [-0.91, -0.42]
to a) 2015	-0.7333 0.12		15	1.4%	0.48 [0.38, 0.61]		Cho a] 2015 -0.1333 0.1007 15 15 2.4% -0.13 [-0.33, 0.06]
io b] 2013	-0.1333 0.10		15	1,4%	0.88 [0.72, 1.07]		Cho b] 2013 -0.7333 0.1205 15 15 2.3% -0.73 [-0.97, -0.50]
to b] 2015	-0.4 0.13		15	1.3%	0.67 [0.52, 0.87]		Cho b] 2015 -0.4 0.1303 15 15 2.3% -0.40 [-0.66, -0.14]
to c] 2015	-0.2667 0.12		15	1,4%	0.77 [0.60, 0.97]		Cho c] 2015 -0.2667 0.1205 15 15 2.3% -0.27 [-0.50, -0.03]
to d] 2015	-0.1333 0.10		15	1,4%	0.68 [0.72, 1.07]		Cho d] 2015 -0.1333 0.1007 15 15 2.4% -0.13 [-0.33, 0.06]
toi 2012	0 0.0		30	1,6%	1,00 [0.94, 1.06]	+	Frey a) 2018 0 0.0494 19 19 2.5% 0.00 [-0.10, 0.10]
oshen 2013	-0.6286 0.0		35	1.5%	0.53 [0.45, 0.63]		Frey b) 2018 0 0.047 20 20 2.5% 0.00 [-0.09, 0.09]
ng a] 2017	-0.7333 0.12		15	1.4%	0,48 [0.38, 0.61]		Jang a) 2017 -0.7333 0.1205 15 15 2.3% -0.73 [-0.97, -0.50]
ing b] 2017	-0.2667 0.12		15	1.4%	0.77 [0.60, 0.97]		Jang b] 2017 -0.2867 0.1205 15 15 2.3% -0.27 [-0.50, -0.03]
ing c) 2017	-0.4 0.13		15	1.3%	0.67 [0.52, 0.87]		Janson aj 2014 -0.6429 0.075 42 42 2.4% -0.64 [-0.79, -0.50]
ing d] 2017	-0.2 0.11		15	1.4%	0.82 [0.66, 1.02]		Jansen b] 2014 -0.7561 0.0689 41 41 2.4% -0.76 [-0.89, -0.62]
insen a] 2014	-0.6429 0.0		42	1.5%	0.53 [0.45, 0.61]		Jeong b] 2012 -0.75 0.1015 20 20 2.4% -0.75 [-0.95, -0.55]
ansen b] 2014	-0.7561 0.06		-41	1.5%	0.47 [0.41, 0.54]		Jung b) 2007 -0.15 0.0879 20 20 2.4% -0.15 [-0.32, 0.02]
eong a] 2012	-0.3684 0.11	7 19	19	1,4%	0,69 [0.55, 0.86]		Larsen b] 2014 -0.3571 0.1328 14 14 2.3% -0.36 [-0.62, -0.10]
ong b] 2012	-0.15 0.08		20	1.5%	0.86 [0.72, 1.02]		Picton aj 2015 -0.4483 0.0938 29 29 2.4% -0.45 [-0.63, -0.26]
a] 2013	-0.3 0.10	2 20	20	1.4%	0.74 [0.60, 0.91]		Schotole a] 2015 -0.64 0.0394 150 150 2.5% -0.64 [-0.72, -0.56]
o b] 2013	-0.25 0.10		20	1.4%	0.78 [0.64, 0.95]		Schotola b] 2015 -0.66 0.0389 150 150 2.5% -0.66 [-0.74, -0.58]
o b] 2014	-0.375 0.07		40	1.5%	0.69 [0.59, 0.80]		Subtotal (95% CI) 625 625 42.6% -0.43 (-0.58, -0.28)
ing a] 2007	-0.1 0.07		20	1.5%	0.90 [0.78, 1.05]		Historogeneity: Tau# = 0.09; Ch# = 310.95, df = 17 (P < 0.00001); P = 95%
ung b] 2007	-0.15 0.05	9 20	20	1.5%	0.86 [0.72, 1.02]		Test for overall effect: Z = 5.68 (P < 0.00001)
oh a] 2013	-0.7333 0.06		30	1.5%	0.48 [0.41, 0.57]		
wsk a] 2010	-0.6538 0.09		26	1,4%	0.52 [0.43, 0.63]		5.2.2 Inhalational
wak a] 2011	-0.2424 0.07		33	1.5%	0.78 [0.67, 0.91]		Choi 2012 0 0.032 30 30 2.5% 0.09 [-0.06, 0.06]
wak a) 2017	-0.45 0.11	6 20	20	1.4%	0.64 [0.51, 0.80]		Hanouz 2016 -0.5472 0.069 53 53 2.4% -0.55 (-0.68, -0.41)
wak b] 2010	-0.28 0.09		25	1.5%	0.76 [0.63, 0.91]		Jang a) 2016 -0.44 0.1011 25 25 2.4% -0.44 [-0.64, -0.24]
wak b] 2011	-0.0303 0.04		33	1.6%	0.97 [0.90, 1.05]	-	Jangb 2016 0.92 0.0653 25 25 2.5% 0.92 [1.05, 0.79]
wak b] 2017	-0.35 0.10		20	1,4%	0.70 [0.57, 0.87]		Jang cj 2017 -0.4 0.1303 15 15 2.3% -0.40 (-0.66, -0.14)
se 2015	-0.175 0.06	8 40	40	1.5%	0.64 [0.74, 0.95]		Jang (2017 0.2 0.1121 15 15 2.3% 0.20(0.42,0.02)
Culloch 2010	-0.5769 0.11	9 19	19	1,4%	0.56 [0.45, 0.70]		Jang 2012 - 0.384 0.1137 19 19 2.3% -0.37[0.50, 0.15]
urtipy b) 2014	-1 0.2		34	0,8%	0.37 [0.21, 0.64]		Jorg 2013 - 0.3 0.1062 20 20 2.3% - 0.31 [0.03, 0.09]
urphy a] 2014	-1 0.2	8 36	36	0.8%	0.37 [0.22, 0.62]	-	Joh 2013 - 0.25 0.105 20 20 2.3% -0.26 [0.01, 0.06]
zturk c) 2015	0 0.0		20	1.6%	1.00 [0.91, 1.10]	-	Jo b) 2013 - 40,55 0,01015 20 22 24% - 40,55 (40,50,50) - Jo b) 2014 - 63,75 0,0076 40 40 40 24% - 63,8 (-653, -622)
chotola a] 2015	-0.64 0.03	4 150	150	1.6%	0.53 [0.49, 0.57]		Job j 2014 - 0.375 0.0776 40 40 2.4% - 0.38[-0.38, -0.22]
chotola bi 2015	-0.65 0.03		150	1,6%	0.52 10.48, 0.561		
ording al 2011	-0.85 0.05		20	1.5%			Koh aj 2013 -0.7333 0.0833 30 30 2.4% -0.73 [-0.90, -0.57] Kwak aj 2010 -0.6538 0.0955 26 26 2.4% -0.65 [-0.84, -0.47]
ubtotal (95% CI)	-2.35 0.05	1113	1113	50.8%	0.43 [0.36, 0.51] 0.66 [0.60, 0.74]	•	Kwaka 2010 -0.6538 0.0955 26 26 2.4% -0.65 [-0.84, -0.47]
	0.09; ChP = 564.74, df = 35 (P < 0.						
est for overall effect: Z	= 7.91 (P < 0.00001)	-90 M. 1.					Kwak a) 2017 - 0.45 0.1136 20 20 2.3% - 0.45 [-0.67, -0.23] Kwak b) 2010 - 0.28 0.0928 25 25 2.4% - 0.28 [-0.46, -0.10]
							Kwak 5) 20100.28 0.0028 25 25 2.4%0.28 (-0.46, -0.10)
.1.2 GA ± ISB							Lee 20150.175 0.0622 40 40 2.5%0.17[-0.30,-0.05]
tengisun aj 2014	0 0.03	1 25	25	1.6%	1.00 [0.93, 1.08]	+	
lengisun b] 2014	0 0.04		23	1.6%	1.00 (0.92, 1.08)	1	Murrhpy b] 2014 -1 0.0284 34 34 2.5% -1.00 [-1.06, -0.94]
Frey a) 2018	0 0.04		19	1.6%	1.00 [0.91, 1.10]	1	Murphy aj 2014 -1 0.0268 36 36 2.5% -1.00 (-1.05, -0.95)
rey b) 2018	0 0.04		20	1.6%	1.00 [0.91, 1.10]	-	Pictor b] 2015 -0.6296 0.0949 27 27 2.4% -0.63 [-0.62, -0.44]
lanouz 2016	-0.5472 0.0		53	1.5%	0.58 [0.51, 0.66]		Seeding a) 2011 -0.85 0.0679 20 20 2.4% -0.85 [-1.02, -0.68]
lang a) 2016	-0.5472 0.0	8 25	25	1,4%	0.68 [0.51, 0.66]		Soeding a) 2013 -0.6471 0.1197 17 17 2.3% -0.65 [-0.88, -0.41]
lang b] 2016	-0.46 0.10		25	1,6%	0.37 [0.34, 0.40]		Seeding b] 2013 0 0.0548 17 17 2.5% 0.00 [-0.11, 0.11]
			25	1.6%	0.37 [0.34, 0.40] 0.70 [0.54, 0.91]		Subtotal (95% CI) 626 626 57.4% -0.46 [-0.64, -0.29]
					1.00 [0.94, 0.91]		Heterogeneity: Tau ² = 0.19; Ch ² = 1100.62; df = 23 (P < 0.00001); l ² = 98%
arsen b) 2014	-0.3571 0.13		00		1.00 (0.97, 1.10)	-	Test for overall effect: $Z = 5.14$ (P < 0.00001)
arsen b) 2014 Ozturk a) 2015	0 0.0	7 20	20	1.6%	4 00 10 04 4 100		
arsen b) 2014 Ozturk a) 2015 Ozturk b) 2015	0 0.0	7 20	20	1.6%	1.00 [0.91, 1.10]		The second
arsen b) 2014 Dzturk a) 2015 Dzturk b) 2015 Noton a) 2015	0 0.0 0 0.0 -0.4483 0.09	7 20 7 20 8 29	20 29	1.6%	0.64 [0.53, 0.77]	T	Total (#5% Cl) 1251 1251 100.0% -0.45 [-0.57, -0.33]
arsen b) 2014 Ozturk a) 2015 Ozturk b) 2015 Picton a) 2015 Picton b) 2015	0 0.0 0 0.0 -0.4483 0.09 -0.6296 0.09	7 20 7 20 8 29 9 27	20 29 27	1.6% 1.4% 1.4%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64]	<u> </u>	
arson b) 2014 Ozturk a) 2015 Ozturk b) 2015 Victon a) 2015 Victon b) 2015 Soeding a) 2013	0 0.0 0 0.0 -0.4483 0.09 -0.6296 0.09 -0.6471 0.11	7 20 7 20 8 29 9 27 7 17	20 29 27 17	1.6% 1.4% 1.4%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66]	<u> </u>	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
ansen b) 2014 zturk a) 2015 zturk b) 2015 (cton a) 2015 (cton b) 2015 oeding a) 2013 oeding b) 2013	0 0.0 0 0.0 -0.4483 0.09 -0.6296 0.09	7 20 7 20 8 29 9 27 7 17 8 17	20 29 27 17	1.6% 1.4% 1.4% 1.4% 1.6%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.00 [0.90, 1.11]	Ē	Heterogeneity: Tau ² = 0.15; Ch ² = 1471.08, df = 41 (P < 0.00001); P = 97%
ansen b) 2014 zturk a) 2015 zturk b) 2015 icton a) 2015 icton b) 2015 oeding a) 2013 oeding b) 2013 ubtotal (95% CI)	0 0.0 0 0.0 -0.4483 0.09 -0.6285 0.09 -0.6471 0.11 0 0.05	7 20 7 20 8 29 9 27 7 17 8 17 334	20 29 27 17 17 334	1.6% 1.4% 1.4%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66]	= _	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
umen b) 2014 zhurk a) 2015 zhurk b) 2015 cton b) 2015 cton b) 2015 beding a) 2013 beding b) 2013 ubtotal (95% CI) aterogoneity: Tau ² = 0	0 0.0 0 0.0 -0.4483 0.09 -0.6471 0.11 0 0.05 -0.6471 0.11 0 0.05	7 20 7 20 8 29 9 27 7 17 8 17 334	20 29 27 17 17 334	1.6% 1.4% 1.4% 1.4% 1.6%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.00 [0.90, 1.11]	= •	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
amen b) 2014 zturk b) 2015 ictor b) 2015 ictor b) 2015 ictor b) 2015 ording b) 2013 ording b) 2013 ubtotal (95% CI) otorogeneity: Tau ² = 0	0 0.0 0 0.0 -0.4483 0.09 -0.6471 0.11 0 0.05 -0.6471 0.11 0 0.05	7 20 7 20 8 29 9 27 7 17 8 17 334	20 29 27 17 17 334	1.6% 1.4% 1.4% 1.4% 1.6%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.00 [0.90, 1.11]	= •	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
anien b) 2014 zhurk b) 2015 icton b) 2015 icton b) 2015 icton b) 2015 beding b) 2013 bbtodal (95% Cl) eterogeneity: Tau ² = 0 est for overall effect: Z	0 0.0 0 0.0 -0.4483 0.09 -0.6471 0.11 0 0.05 -0.6471 0.11 0 0.05	7 20 7 20 8 29 9 27 7 17 8 17 334	20 29 27 17 17 334	1.6% 1.4% 1.4% 1.4% 1.6%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.00 [0.90, 1.11]	= •	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
amen b) 2014 zburk b) 2015 Voton b) 2015 Voton b) 2015 Voton b) 2015 voton b) 2015 voton b) 2013 voton b) 2015 voton b	0 0.0 0.0 0.4463 0.95 0.4463 0.95 0.4463 0.95 0.4671 0.11 0 0.05 0.15; ChP = 650.04, df = 13 (P < 0.5 c = 2.74 (P = 0.006)	7 20 7 20 8 29 9 27 7 17 8 17 334 0001): P	20 29 27 17 17 334 = 98%	1.6% 1.4% 1.4% 1.4% 1.6% 21.1%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.00 [0.80, 1.11] 0.75 [0.61, 0.92]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
anien b) 2014 zburk b) 2015 zburk b) 2015 loton b) 2015 loton b) 2015 coding b) 2013 outing b) 2015 coding b) 2015 cod	0 0.0 0.0.4483 0.09 -0.4485 0.09 -0.6473 0.11 0 0.05 0.15; ChP = 650.04, df = 13 (P < 0) = 2.74 (P = 0.006) 0 0.00	7 20 7 20 8 29 9 27 7 17 8 17 334 0001): P	20 29 27 17 17 334 = 98%	1.6% 1.4% 1.4% 1.6% 21.1%	0.64 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.00 [0.90, 1.11] 0.75 [0.61, 0.92]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
anian b) 2014 zhark b) 2015 Extrik b) 2015 Extrik b) 2015 Extrik b) 2015 Deding b) 2013 Deding b) 2013 Deding b) 2013 Deticted (195% CI) elarogeneity: Tau ² = 0 Ext for overall effect: Z 1.3 ISB ± sedation asaran 2017 hierichiai g) 2015	0 0.0 0.0.40 -0.4295 0.09 -0.4295 0.09 -0.4295 0.09 -0.4210 0.11 0 0.05 0.15; Chi ^a = 650.04, df = 13 (P < 0. c = 2.74 (P = 0.006) 0 0.05	7 20 7 20 8 29 9 27 7 17 8 17 334 (0001); P 2 30 7 59	20 29 27 17 17 334 = 98%	1.6% 1.4% 1.4% 1.6% 21.1%	0.64 [0.53, 0.77] 0.53 [0.44, 0.66] 0.52 [0.41, 0.66] 1.00 [0.84, 0.05] 1.00 [0.84, 1.05] 0.78 [0.69, 0.87]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
amion b) 2014 zzturk a) 2015 zzturk b) 2015 icton b) 2015 oeding b) 2013 ubtobal (95% CI) vatorogeneity: Tau ² = 0 est for overail effect: Z 	0 0.0 0 0.0 -0.443 0.05 -0.6248 0.05 -0.6471 0.11 0 0.05 2.15; ChP = 650.04, df = 13 (P < 0. 2 = 2.74 (P = 0.006) 0 0.07 -0.2542 0.05 -0.0433 0.03	7 20 7 20 8 29 9 27 7 17 8 17 334 (0001); P 2 30 7 58 4 60	20 29 27 17 17 334 = 98% 30 59 60	1.6% 1.4% 1.4% 1.4% 1.6% 21.1%	0.64 [0.53, 0.77] 0.53 [0.44, 0.66] 1.00 [0.30, 1.11] 0.75 [0.61, 0.92] 1.00 [0.94, 1.06] 0.78 [0.69, 0.07] 0.78 [0.49, 0.07]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
amen b) 2014 Julix a) 2015 Julix b) 2015 Julix b) 2015 John D) 2015 John D) 2015 John D) 2015 John D) 2013 Jub John D) 2013 Jub John D) 2013 Jub John D) 2013 Jub John D) 2015 John D) 2015 John D) 2015 John D) 2015	0 0.0 0.0.4 0.0.43 0.05 -0.4245 0.05 -0.4245 0.05 -0.4247 0.11 0 0.05 0.15; ChP = 650.04, of = 13 (P < 0. c = 2.74 (P = 0.006) 0 0.0 0 0.0 -0.2542 0.05 -0.0433 0.03 -0.0421 0.03	7 20 7 20 8 29 9 27 7 17 8 17 334 (0001); P 2 30 7 58 4 60 7 49	20 29 27 17 334 = 98% 30 59 60 49	1,6% 1,4% 1,4% 1,6% 21,1% 1,6% 1,5% 1,6%	0.54 [0.53, 0.77] 0.53 [0.44, 0.66] 0.52 [0.41, 0.66] 1.00 [0.30, 1.11] 0.75 [0.61, 0.92] 1.00 [0.94, 1.06] 0.78 [0.68, 0.67] 0.62 [0.85, 0.69] 0.54 [0.87, 1.01]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
near b) 2014 zhak a) 2015 zhak b) 2015 toton b) 2015 toton b) 2015 cotin b) 2015 cotin b) 2015 cotin b) 2015 cotin b) 2015 cotin b) 2015 cotin b) 2015 starce and refet. Z 1.3 ISB ± sedation asama 2017 thierchish aj 2015 sasanen b) 2015	0 0.0 0 0.0 0.0483 0.05 -0.0471 0.11 0.0528 0.05 -0.0471 0.11 0 0.05 0.15; ChP = 650.04, df = 13 (P < 0. 2.274 (P = 0.006) 0 0.07 -0.2542 0.05 -0.0432 0.05 -0.0432 0.05 -0.042 0.05	7 20 7 20 8 29 9 27 7 17 8 17 334 0001): P 2 30 7 59 4 60 7 49 8 50	20 29 27 17 334 = 98% 30 59 60 49 50	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6%	0.44 [0.53, 0.77] 0.53 [0.44, 0.66] 0.52 [0.41, 0.66] 1.00 [0.50, 1.11] 0.75 [0.64, 0.92] 1.00 [0.94, 1.06] 0.78 [0.68, 0.87] 0.42 [0.85, 0.89] 0.44 [0.87, 1.01]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
ansen (b) 2014 Luturk (a) 2015 Luturk (b) 2015 Luturk (b) 2015 Loton (b) 2016 Loton (b) 2016 Loton (b) 2016 Loton (b) 2013 Lutotal (b) 2013 Lutotal (b) 2014 Luturk (b) 2015 Luturk (b) 2016 Luturk (b) 2016	0 0.0. 0 0.0. 0.4.483 0.05 0.6.25 0.05 0.6.27 0.01 0 0.05 0.15, CeP = 660.04, df = 13 (P < 0. 0 0.5 0.15, CeP = 660.04, df = 13 (P < 0. 0 0.05 0 0.05 0 0.001 0.03 0 0.011 0.03 0.016 0.03 0.012 0.03 0.024 0.05	7 20 7 20 8 29 9 27 7 8 17 334 0001); P 2 30 7 59 4 60 7 59 4 60 7 49 8 50 3 49	20 29 27 17 334 = 98% 30 59 60 49 50 49	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.5% 1.6% 1.6%	0.54 [0.53, 0.77] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.00 [0.94, 1.06] 1.00 [0.94, 1.06] 0.75 [0.81, 0.92] 1.00 [0.94, 1.06] 0.78 [0.86, 0.87] 0.62 [0.85, 0.89] 0.54 [0.87, 1.01] 0.52 [0.73, 0.92]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
anion (b) 2014 Juhik (a) 2015 Juhik (b) 2015 Juhik	0 0.0 0.0 0.4483 038 0.4483 038 0.4483 038 0.4483 038 0.4483 038 0.4547 01 0.055 0.0	7 20 7 20 8 29 9 27 7 17 334 0001): P 2 30 7 59 4 60 7 49 8 50 3 49 7 64	20 29 27 17 334 = 98% 30 59 60 49 50 49 64	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.6% 1.6%	0.44 [0.53, 0.77] 0.53 [0.44, 0.66] 1.00 [0.90, 1.11] 0.75 [0.64, 0.92] 1.00 [0.94, 1.06] 0.78 [0.64, 0.92] 0.75 [0.67, 0.92] 0.74 [0.87, 0.01] 0.42 [0.77, 0.01] 0.52 [0.73, 0.92] 0.75 [0.66, 0.84]	¹ ¹ ¹ ¹ + ¹ ¹ ¹ ¹	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
neen b) 2014 Junk a) 2015 Junk a) 2015 Junk b) 2015 Joton a) 2015 Joton a) 2015 Joton a) 2015 Joton a) 2013 Joton a) 2013 Joton a) 2013 Joton a) 2014 Joton a) 2015 Joton	0 0.0 0.0 0.4483 009 0.4483 009 0.4483 009 0.4571 011 0.4571 011000000000000000000000000000000000	7 20 7 20 8 29 9 27 7 17 8 17 334 (0001): P 7 59 7 59 7 59 8 50 7 49 8 50 3 49 7 64 2 30	20 29 27 17 334 = 98% 30 59 60 49 50 49 50 49 50 49 50 49 50	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6%	0.44 [0.53, 0.77] 0.53 [0.44, 0.66] 0.52 [0.44, 0.66] 1.00 [0.90, 1.11] 0.75 [0.84, 1.06] 0.75 [0.84, 0.87] 0.78 [0.88, 0.87] 0.48 [0.87, 1.01] 0.44 [0.87, 1.01] 0.44 [0.87, 1.01] 0.42 [0.87, 1.01] 0.42 [0.87, 1.01] 0.42 [0.87, 1.01] 0.42 [0.87, 1.01] 0.42 [0.87, 1.01] 0.42 [0.87, 1.01] 0.45 [0.87, 0.02] 0.75 [0.80, 0.80] 0.50 [0.80, 1.02]		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
union ib (2014 zuhuk a) 2015 zuhuk (2) 2015 toton a) 2015 toto	0 0.00 0.00 -0.4485 0.05 -0.6286 0.05 -0.6286 0.05 -0.6286 0.05 -0.6286 0.05 -0.6287 0.05 -0.6286 0.05 -0.033 0.03 -0.0482 0.05 -0.0482 0.05 -0.0482 0.05 -0.0482 0.05 -0.0481 0.05 -0.0481 0.05 -0.0481 0.05 -0.0481 0.05 -0.0481 0.05 -0.0481 0.05 -0.0481 0.05 -0.0481 0.05 -0.0481 0.05 -0.0482 0.05 -0.	7 20 7 20 8 29 9 27 7 17 8 17 334 60001); P 2 30 7 59 4 60 7 59 4 60 7 59 4 60 7 49 8 50 3 49 7 64 2 30 2 49	20 29 27 17 334 = 98% 30 59 60 49 50 49 64 49 64 49	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.5% 1.6%	$\begin{array}{c} 0.4 \left[0.53, 0.77 \right] \\ 0.53 \left[0.44, 0.64 \right] \\ 0.52 \left[0.41, 0.66 \right] \\ 0.62 \left[0.41, 0.66 \right] \\ 0.75 \left[0.41, 0.66 \right] \\ 0.75 \left[0.41, 0.69 \right] \\ 0.75 \left[0.48, 0.87 \right] \\ 0.42 \left[0.87, 101 \right] \\ 0.52 \left[0.73, 0.82 \right] \\ 0.57 \left[0.46, 0.84 \right] \\ 0.59 \left[0.80, 0.10 \right] \\ 0.59$		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
neen b) 2014 Junk a) 2015 Junk b) 2015 Junk b) 2015 Joton a) 2015 Joton a) 2015 Joton a) 2015 Joton a) 2013 Jotof a) 2013 Jotof a) 2013 Jotof a) 2014 Jotof a) 2014 Jotof a) 2014 Jotof a) 2015 Jotof a) 2015 Jotof a) 2015 Jotof a) 2015	0 0.00 0.04485 005 0.050 0.050 0.055 0.0571 0.11 0.055 0.	7 20 7 20 8 29 9 27 7 17 8 17 334 6001); P 2 30 7 58 4 60 7 49 8 50 3 49 8 50 3 49 7 64 2 30 2 49 8 7 49	20 29 27 17 334 = 98% 30 59 60 49 50 49 64 30 49 49	1,6% 1,4% 1,4% 1,4% 1,6% 21,1% 1,6% 1,5% 1,6% 1,6% 1,5% 1,5% 1,5% 1,5%	0.64 [0.53, 0.77] 0.53 [0.44, 0.66] 0.57 [0.44, 0.66] 1.00 [0.60, 1.06] 1.00 [0.64, 0.66] 1.00 [0.64, 0.67] 0.78 [0.68, 0.67] 0.27 [0.68, 0.67] 0.24 [0.67, 101] 0.34 [0.67, 101] 0.34 [0.67, 101] 0.34 [0.67, 103] 0.58 [0.58, 0.68] 0.58 [0.53, 0.56] 0.54 [0.50, 0.56]	+ +++++++++++++++++++++++++++++++++++	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
near b) 2014 durk a) 2015 durk b) 2015 clon b) 2015 clon b) 2015 clon b) 2015 dots b) 2013 seding b) 2013 seding b) 2013 seding b) 2013 seding b) 2013 seding b) 2015 seamen b) 2015 seamen b) 2015 seamen 2015 sea	0 0.0 0.0 0.4483 00 0.4483 00 0.4483 00 0.4483 00 0.4584 00 0.4584 00 0.4584 00 0.4584 00 0.058 000000000000000000000000000000	7 20 7 20 8 29 9 27 7 17 8 17 334 6001), P 2 30 7 59 4 6 60 7 59 8 50 3 49 7 64 2 30 2 49 8 50 3 49 4 5 6 8 50 8 50 8 50 8 50 8 50 8 50 8 50 8 50	20 29 27 17 334 = 98% 30 50 49 50 49 50 49 50 49 50 49 50 49 55	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.6% 1.6% 1.5% 1.5% 1.5% 1.5%	0.44 [0.53, 0.77] 0.53 [0.44, 0.66] 0.57 [0.44, 0.66] 0.57 [0.44, 0.66] 1.00 [0.90, 1.11] 0.75 [0.44, 0.92] 1.00 [0.94, 1.06] 0.74 [0.45, 0.87] 0.42 [0.85, 0.89] 0.44 [0.87, 1.01] 0.52 [0.75, 0.68] 0.44 [0.87, 1.01] 0.52 [0.75, 0.68] 0.54 [0.75, 0.68] 0.56 [0.71, 0.80] 0.56 [0.71, 0.80] 0.56 [0.51, 0.80] 0.56 [0.55, 0	 	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
near b) 2014 zulk a) 2015 zulk b) 2015 toton a) 2015 assamin a) 2014 assamin a) 2014 assamin a) 2014 assamin a) 2014 assamin a) 2015 alam a) 2015 toton a) alam a) 2015 toton a) toton a) t	0 0.00 0.04483 008 0.05480 008 0.05481 008 0.055 0.0558 0.0558 0.055 0.	7 20 7 20 8 29 9 27 7 17 8 17 334 0001), P 2 30 7 59 8 50 3 49 8 50 3 49 7 49 8 50 3 49 7 49 8 55 55 55	20 29 27 17 17 334 = 98% 59 60 49 60 49 60 49 60 49 60 49 60 49 55 55	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.5% 1.6% 1.6% 1.5% 1.6% 1.5% 1.6% 1.5% 1.6% 1.5%	0.46 [0.53, 0.77] 0.53 [0.44, 0.64] 0.55 [0.44, 0.64] 1.00 [0.90, 1.61] 0.75 [0.64], 0.92] 1.00 [0.94, 1.06] 0.75 [0.94], 0.92] 0.75 [0.94], 0.97] 0.75 [0.94], 0.97] 0.75 [0.94], 0.97] 0.75 [0.96], 0.97]	<u> </u>	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
near b) 2014 zulk a) 2015 zulk b) 2015 toton a) 2015 assamin a) 2014 assamin a) 2014 assamin a) 2014 assamin a) 2014 assamin a) 2015 alam a) 2015 toton a) alam a) 2015 toton a) toton a) t	0 0.0 0.0 0.4483 00 0.4483 00 0.457 0 0.0 0.457 0 0.0 0.55 CHF = 660.04, d' = 13 (P = 0. -2.2452 006) 0 0.0 -2.2452 005 -0.04212 0.0 -0.0412 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.0412 0.0 -0.0	7 20 7 20 8 29 9 27 7 17 8 17 334 0001): P 2 30 7 49 8 50 7 49 8 50 7 64 2 30 7 64 2 30 7 64 2 30 7 64 2 30 7 64 2 30 7 19 8 55 2 55 1 20	20 29 27 17 17 334 = 98% 30 59 60 49 60 49 64 30 49 64 30 49 55 55 55 520	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.5% 1.5% 1.5% 1.6% 1.5% 1.6%	0.46 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.52 [0.44, 0.64] 1.00 [0.84, 1.06] 0.77 [0.64], 0.82] 0.78 [0.64], 0.82] 0.78 [0.68, 0.67] 0.44 [0.87, 101] 0.44 [0.87, 101] 0.45 [0.87, 0.82] 0.76 [0.46, 0.84] 0.45 [0.87, 0.82] 0.76 [0.46, 0.84] 0.45 [0.87, 0.82] 0.45 [0	, ¹ 1, ¹	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
near b) 2014 zulk a) 2015 zulk b) 2015 toton a) 2015 toton a) 2015 toton a) 2015 toton a) 2015 toton a) 2015 toton 201	0 0.0 0 0.0 0.4445 0.05 0.4445 0.05 0.4445 0.05 0.4547 0.01 0.55 0.06 0.4547 0.01 0.4547 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4524 0.05 0.4254 0.05 0.455 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.05	7 20 7 20 8 29 9 27 7 17 8 17 8 17 8 334 0001), P 2 300 7 59 4 60 7 59 4 60 7 59 4 60 7 59 4 60 7 59 8 50 2 30 2 49 8 50 2 30 2 49 8 50 2 30 7 50 8 50 7 17 8 19 8 50 8 50	20 29 27 17 334 = 98% 30 59 60 49 50 49 50 49 55 55 55 55 20 40	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.5% 1.6% 1.5% 1.6% 1.5% 1.5% 1.6% 1.5% 1.6%	0.46 [0.53, 0.77] 0.53 [0.44, 0.66] 0.53 [0.44, 0.66] 0.57 [0.44, 0.66] 1.00 [0.90, 1.11] 0.75 [0.64], 0.92] 1.00 [0.94, 1.06] 0.74 [0.96, 0.99] 0.44 [0.97], 101] 0.45 [0.97, 1.11] 0.45 [0.97, 1.11] 0.45 [0.97, 1.11] 0.45 [0.97, 1.11] 0.45 [0.97, 0.96] 0.46 [0.97, 0.96] 0.46 [0.97, 0.96] 0.46 [0.97, 0.96] 0.46 [0.97, 0.96] 0.46 [0.97, 0.96] 0.47 [0.97, 0.96] 0.48 [0.97, 0.96] 0.49 [0.77,	, ¹	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
ansen bj 2014 zutik aj 2015 statik bj 2015 iston aj 2015 iston bj 2015 iston bj 2015 oeding aj 2013 oeding aj 2013 oeding aj 2013 oeding aj 2013 istongenerik aj 2015 istongenerik aj 2015 istongenerik aj 2015 istana bj 2014 asannen cj 2014 asannen cj 2015 is aj 2003 is aj 2003 oeding bj 2011 oeding 2011	0 0.0 0.0 0.4483 00 0.4483 00 0.457 0 0.0 0.457 0 0.0 0.55 CHF = 660.04, d' = 13 (P = 0. -2.2452 006) 0 0.0 -2.2452 005 -0.04212 0.0 -0.0412 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.2481 0.0 -0.0412 0.0 -0.0	7 20 7 20 8 29 9 27 7 17 8 17 8 17 8 334 0001), P 2 300 7 59 4 60 7 59 4 60 7 59 4 60 7 59 4 60 7 59 8 50 2 30 2 49 8 50 2 30 2 49 8 50 2 30 7 50 8 50 7 17 8 19 8 50 8 50	20 29 27 17 17 334 = 98% 30 59 60 49 60 49 64 30 49 64 30 49 55 55 55 520	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.5% 1.5% 1.5% 1.6% 1.5% 1.6%	0.46 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.52 [0.44, 0.64] 1.00 [0.84, 1.06] 0.77 [0.64], 0.82] 0.78 [0.64], 0.82] 0.78 [0.68, 0.67] 0.44 [0.87, 101] 0.44 [0.87, 101] 0.45 [0.87, 0.82] 0.76 [0.46, 0.84] 0.45 [0.87, 0.82] 0.76 [0.46, 0.84] 0.45 [0.87, 0.82] 0.45 [0	 	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
anismi b) 2014 attirk a) 2015 statirk (a) 2015 iston a) 2015 iston a) 2016 iston a) 2016 iston a) 2016 iston a) 2016 astir for annual and a astir for annual all and a astir for annual all and a astir for annual all and astir for annual annual a astir for annual annual a astir for annual annual a 2016 astir for annual annual a 2016 astir for annual annual a 2016 astir for annual annual a 2016 astir for annual a 2017 annual a 2011 annual a 2011 a	0 0.0 0 0.0 0.4445 0.05 0.4445 0.05 0.4445 0.05 0.4547 0.01 0.55 0.06 0.4547 0.01 0.4547 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4542 0.05 0.4524 0.05 0.4254 0.05 0.455 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.055 0.05	7 20 7 20 8 29 9 27 7 17 8 334 6001): P 2 300 7 59 4 60 7 49 8 49 7 49 8 49 7 64 2 30 2 49 7 49 8 55 2 55 1 20 6 40 5 55 1 20 6 40 7 49 8 55 6 55 1 20 8 55 1 20 8 17 8 19 8 19 1	20 29 27 17 334 = 98% 30 59 60 49 50 49 50 49 55 55 55 55 20 40	1.6% 1.4% 1.4% 1.6% 21.1% 1.6% 1.5% 1.6% 1.5% 1.6% 1.5% 1.5% 1.6% 1.5% 1.6%	0.44 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.52 [0.41, 0.65] 1.00 [0.84, 1.00] 0.75 [0.64], 0.92] 1.00 [0.84, 1.00] 0.76 [0.64], 0.87] 0.76 [0.85, 0.87] 0.44 [0.87, 1.01] 0.44 [0.87, 1.01] 0.44 [0.87, 1.01] 0.44 [0.87, 1.01] 0.44 [0.87, 1.01] 0.44 [0.87, 1.01] 0.45 [0.76, 0.96] 0.76 [0.86, 0.86] 0.76 [0.86,		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
amen 0 2014 amen 0 2015 total 2013 total 2013 total 2015 total 2015 tota	0 0.0 0 0.0 0.4483 009 0.4693 009 0.4693 009 0.4693 009 0.4693 009 0.4693 009 0.4593 009 0.4593 009 0.4593 009 0.42842 005 0.4084 0.05 0.42843 005 0.42843 005	7 20 7 20 8 29 9 27 7 17 334 6001), P 2 30 7 59 8 50 3 49 7 64 8 50 3 49 7 64 8 50 3 49 2 30 2 49 8 55 2 55 1 20 6 55 5 2 40 6 55 2 40 2 40	20 29 27 17 354 = 98% 30 59 60 49 50 49 64 30 49 55 55 55 20 40 40 40	1.6% 1.4% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6%	0.46 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 1.00 [0.94, 1.01] 0.75 [0.84, 0.64] 1.00 [0.94, 1.01] 0.75 [0.84, 0.67] 0.26 [0.85, 0.69] 0.26 [0.85, 0.69] 0.26 [0.85, 0.69] 0.27 [0.86, 0.84] 0.75 [0.86, 0.86] 0.75 [0.86, 0.86] 0.75 [0.86, 0.86] 0.75 [0.86, 0.86] 0.75 [0.86, 0.86] 0.75 [0.86, 0.86] 0.75 [0.76, 0.86] 0.75 [0.86, 0	1111 + 1111 + 111 + 111 + 111 + 111 + 111 + 111 + 111 + 111 + 111 + 111	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
amen 0 2014 amen 0 2015 status 0 2011 status 0 2015 status 0 2011 status 0 2011 status 0 2015 status 0 2011 status 0 2015 status 0 2011 status 0 2011 status 0 2015 status 0 2011 status 0 2015 status 0 2011 status 0 2015 status 0 2011 status 0 2015 status 0 2	0 0.00 0.04485 005 0.05485 005 0.05487 0 055 0.0557 0 0055 0.055 0 0055 0.055 0 0055 0.053 005 0.053 005 0.053 005 0.051 005 0.055 0	7 20 7 20 8 29 9 27 7 17 8 334 0001): P 2 30 7 59 8 50 3 49 8 50 3 49 8 50 3 49 8 50 3 49 7 64 2 49 7 64 2 49 8 50 2 49 8 50 2 49 8 50 2 40 8 10 7 49 8 50 2 49 8 10 7 49 8 10 7 50 7 40 8 10 7 40 8 10 7 40 8 10 7 40 7 40 8 10 7 40 7 40 7 40 7 40 7 40 7 40 7 40 7 4	20 29 17 17 334 = 98% 30 59 60 49 60 49 60 49 60 49 64 30 55 55 55 20 40 40 40 40	1.6% 1.4% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.6% 1.5% 1.5% 1.5% 1.5% 1.5% 1.5% 1.5% 1.5	0.44 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 1.09 [0.84, 1.11] 0.75 [0.87, 8.28] 1.09 [0.94, 1.00] 0.75 [0.86, 0.89] 0.49 [0.87, 1.01] 0.49 [0.87, 0.05] 0.49 [0.47, 0	, 11, 11, 11, 11, 11, 11, 11, 11, 11, 1	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
ansan b) 2014 zutar (a) 2015 totan (a) 2015 totan (a) 2015 totan (a) 2015 totan (a) 2013 useding (a) 2014 assance (a) 2014 assance (a) 2014 assance (a) 2014 assance (a) 2015 alam (a) 2	0 0.0 0 0.0 0.4483 009 0.4693 009 0.4693 009 0.4693 009 0.4693 009 0.4693 009 0.4593 009 0.4593 009 0.4593 009 0.42842 005 0.4084 0.05 0.42843 005 0.42843 005	7 20 7 20 8 29 9 27 7 17 8 334 0001): P 2 30 7 59 8 50 3 49 8 50 3 49 8 50 3 49 8 50 3 49 7 64 2 49 7 64 2 49 8 50 2 49 8 50 2 49 8 50 2 40 8 50 7 40 7 40 8 50 7 40 7 40 8 50 7 40 7 40 7 40 7 40 7 40 7 40 7 40 7 4	20 29 27 17 354 = 98% 30 59 60 49 50 49 64 30 49 55 55 55 20 40 40 40	1.6% 1.4% 1.4% 1.4% 1.6% 21.1% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6%	0.49 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.52 [0.44, 0.64] 1.59 [0.44, 0.64] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.54] 0.75 [0.46, 0.58] 0.76 [0.46, 0.58] 0.76 [0.46, 0.58] 0.77 [0.46, 0	• + + + + + + + + + + + + + + + + + + +	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
man b) 2014 trus a) 2015 trus b) 2015 trus b) 2015 trus b) 2015 trus b) 2015 testing b) 2015 testing b) 2013 testing b) 2014 testing b) 2015 testing	0 0.0 0 0.0 0.4483 00 0.4483 00 0.4483 00 0.4483 00 0.4483 00 0.4483 00 0.0 0.0 0.0 0.0 0.0 0.0 0.0	7 20 7 20 8 29 9 27 7 17 334 6 17 334 6 17 334 6 17 334 6 17 334 6 17 334 6 17 334 7 58 9 2 7 58 9 2 7 49 9 3 49 9 2 9 2 9 2 7 17 334 4 90 7 58 9 27 7 17 334 4 90 7 58 9 27 7 17 34 4 90 7 58 9 27 7 17 34 4 90 7 58 9 27 7 17 7 17 7 17 7 17 7 17 7 17 7 17 7	20 29 27 17 324 30 59 60 59 60 60 64 49 60 64 49 64 49 55 55 20 40 40 40 40 919	1.6% 1.4% 1.4% 1.6% 1.6% 21.1% 1.6% 1.5% 1.6% 1.5% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.5% 1.6%	0.44 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 1.09 [0.84, 1.11] 0.75 [0.87, 8.28] 1.09 [0.94, 1.00] 0.75 [0.86, 0.89] 0.49 [0.87, 1.01] 0.49 [0.87, 0.05] 0.49 [0.47, 0	++++++++++++++++++++++++++++++++++++++	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
men is 2014 itui aj 2015 itui aj 2013 itui aj 2013 itui aj 2014 itui aj 2014 itu	0 0.0 0.0 0.4483 00 0.0 0.05471 0.0 0.05 0.05	7 20 7 20 8 29 9 27 7 17 334 6 17 334 6 17 334 6 17 334 6 17 334 6 17 334 6 17 334 7 58 9 2 7 58 9 2 7 49 9 3 49 9 2 9 2 9 2 7 17 334 4 90 7 58 9 27 7 17 334 4 90 7 58 9 27 7 17 34 4 90 7 58 9 27 7 17 34 4 90 7 58 9 27 7 17 7 17 7 17 7 17 7 17 7 17 7 17 7	20 29 27 17 324 30 59 60 59 60 60 64 49 60 64 49 64 49 55 55 20 40 40 40 40 919	1.6% 1.4% 1.4% 1.6% 1.6% 21.1% 1.6% 1.5% 1.6% 1.5% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.5% 1.6%	0.49 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.52 [0.44, 0.64] 1.59 [0.44, 0.64] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.54] 0.75 [0.46, 0.58] 0.76 [0.46, 0.58] 0.76 [0.46, 0.58] 0.77 [0.46, 0	• + + + + + + + + + + + + + + + + + + +	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
men is 2014 itui aj 2015 itui aj 2013 itui aj 2013 itui aj 2014 itui aj 2014 itu	0 0.0 0.0 0.4483 00 0.0 0.05471 0.0 0.05 0.05	7 20 7 20 8 29 9 27 7 17 334 6 17 334 6 17 334 6 17 334 6 17 334 6 17 334 6 17 334 7 58 9 2 7 58 9 2 7 49 9 3 49 9 2 9 2 9 2 7 17 334 4 90 7 58 9 27 7 17 334 4 90 7 58 9 27 7 17 34 4 90 7 58 9 27 7 17 34 4 90 7 58 9 27 7 17 7 17 7 17 7 17 7 17 7 17 7 17 7	20 29 27 17 324 30 59 60 59 60 60 64 49 60 64 49 64 49 55 55 20 40 40 40 40 919	1.6% 1.4% 1.4% 1.6% 1.6% 21.1% 1.6% 1.5% 1.6% 1.5% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.5% 1.6%	0.49 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.52 [0.44, 0.64] 1.59 [0.44, 0.64] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.52] 1.59 [0.44, 0.54] 0.75 [0.46, 0.58] 0.76 [0.46, 0.58] 0.76 [0.46, 0.58] 0.77 [0.46, 0	++++++++++++++++++++++++++++++++++++++	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
nmin 12 2014 titik 2015 titik 2015 titi	0 0.0 0.0 0.4483 00 0.0 0.05471 0.0 0.05 0.05	7 20 7 20 8 29 9 27 7 7 8 17 334 7 7 8 17 314 7 334 8 50 7 58 8 50 7 49 8 50 8 50 7 49 8 50 7 49 8 50 7 49 7 49 8 55 1 20 9 19 7 7 7 0 9 10 7 10 7 10 7 10 7 10 8 10 9 10 9 10 9 10 9 10 9 10 9 10 9 10 9	20 29 27 17 324 30 59 60 59 60 60 64 49 60 64 49 64 49 55 55 20 40 40 40 40 919	1.6% 1.4% 1.4% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6	0.49 [0.53, 0.77] 0.53 [0.44, 0.64] 0.53 [0.44, 0.64] 0.52 [0.41, 0.66] 1.57 [0.44, 0.84] 1.57 [0.44, 0.84] 1.57 [0.44, 0.84] 1.57 [0.44, 0.84] 0.75 [0.44, 0.84] 0.75 [0.46, 0.84] 0.76 [0.46, 0.84] 0.77 [0.46, 0.84] 0.76 [0.46, 0.84] 0.76 [0.46, 0.84] 0.76 [0.46, 0.84] 0.77 [0.46, 0.46] 0.46 [0.46, 0.46] 0.46 [0.46, 0.46] 0.76 [0.46, 0.46] 0.77 [0.46, 0.46] 0.76 [0.46, 0.46] 0.76 [0.46, 0.46] 0.77 [0.46, 0.46] 0.76 [0.46, 0	• • • • • • • • • • • • • • • • • • •	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
men is 2014 studie 3, 2015 studie 1, 2015 s	0 0.0 0.0 0.4483 00 0.0 0.05471 0.0 0.05 0.05	7 20 7 20 8 29 9 27 7 8 17 8 17 7 59 9 27 7 59 9 20 7 49 8 50 7 49 8 50 7 49 8 50 7 49 8 50 7 49 8 50 7 49 8 50 7 49 7 49 8 50 7 49 8 50 7 59 9 27 7 7 59 9 29 7 7 59 9 20 7 7 50 9 20 7 7 50 9 20 7 7 50 9 20 7 7 50 9 50 7 7 50 7 7 50 9 50 7 7 50 7 7 50 9 50 7 7 7 50 7 7	20 29 27 17 334 30 59 60 49 60 49 64 49 64 49 55 55 20 40 40 40 40 919 919 919 919 919	1.6% 1.4% 1.4% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6	0.44 [0.53, 0.77] 0.53 [0.44, 0.66] 0.53 [0.44, 0.66] 0.53 [0.44, 0.66] 0.57 [0.64, 0.71] 0.75 [0.64, 0.71] 0.75 [0.64, 0.87] 0.75 [0.64, 0.87] 0.75 [0.66, 0.88] 0.44 [0.87, 101] 0.82 [0.85, 0.88] 0.44 [0.87, 101] 0.82 [0.75, 0.98] 0.49 [0.77, 0.97] 0.82 [0.76, 0.86] 0.97 [0.86, 0.84] 0.97 [0.86, 0.84] 0.97 [0.86, 0.84] 0.97 [0.96, 0.88] 0.98 [0.77, 0.97] 0.76 [0.66, 0.88] 0.48 [0.77, 0.97] 0.76 [0.66, 0.88] 0.48 [0.77, 0.97] 0.76 [0.66, 0.88] 0.48 [0.77, 0.97] 0.48 [0.77, 0.9	+ + + + + + + + + + + + + + + + + + +	Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay
men is 2014 tria 2015 tria 2016 tria 2017 tria 2017	0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0	7 20 7 20 8 29 9 27 7 8 17 8 17 7 59 9 27 7 59 9 20 7 49 8 50 7 49 8 50 7 49 8 50 7 49 8 50 7 49 8 50 7 49 8 50 7 49 7 49 8 50 7 49 8 50 7 59 9 27 7 7 59 9 29 7 7 59 9 20 7 7 50 9 20 7 7 50 9 20 7 7 50 9 20 7 7 50 9 50 7 7 50 7 7 50 9 50 7 7 50 7 7 50 9 50 7 7 7 50 7 7	20 29 27 17 334 30 59 60 49 60 49 64 49 64 49 55 55 20 40 40 40 40 919 919 919 919 919	1.6% 1.4% 1.4% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6	0.44 [0.53, 0.77] 0.53 [0.44, 0.66] 0.53 [0.44, 0.66] 0.53 [0.44, 0.66] 0.57 [0.64, 0.71] 0.75 [0.64, 0.71] 0.75 [0.64, 0.87] 0.75 [0.64, 0.87] 0.75 [0.66, 0.88] 0.44 [0.87, 101] 0.82 [0.85, 0.88] 0.44 [0.87, 101] 0.82 [0.75, 0.98] 0.49 [0.77, 0.97] 0.82 [0.76, 0.86] 0.97 [0.86, 0.84] 0.97 [0.86, 0.84] 0.97 [0.86, 0.84] 0.97 [0.96, 0.88] 0.98 [0.77, 0.97] 0.76 [0.66, 0.88] 0.48 [0.77, 0.97] 0.76 [0.66, 0.88] 0.48 [0.77, 0.97] 0.76 [0.66, 0.88] 0.48 [0.77, 0.97] 0.48 [0.77, 0.9		Haterogeneity: Tau? = 0.15; Ch? = 1471.08, df = 41 (P < 0.00001); P = 97%, Test for overall effect: Z = 7.27 (P < 0.00001) BC/D Suplay

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 \pm 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 \pm sedation (test for sub-group differences P = 0.0007, $f^2 = 86.2\%$). However, higher observed risk was not found for subjects of TIVA-propofol over inhaled anaesthetics for developing hypotensive responses (P = 0.76, $f^2 = 0\%$). 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 = 34%, 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 (P = 0.004, F = 87.7%). 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; rSO₂ - Regional cerebral oxygen saturation. SE - Standard error; TIVA - Total intravenous anaesthesia