Association of intraoperative hypotension with postoperative morbidity and mortality: systematic review and meta-analysis

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Abstract

Background: Intraoperative hypotension, with varying definitions in literature, may be associated with postoperative complications. The aim of this meta-analysis was to assess the association of intraoperative hypotension with postoperative morbidity and mortality.

Methods: MEDLINE, Embase and Cochrane databases were searched for studies published between January 1990 and August 2018. The primary endpoints were postoperative overall morbidity and mortality. Secondary endpoints were postoperative cardiac outcomes, acute kidney injury, stroke, delirium, surgical outcomes and combined outcomes. Subgroup analyses, sensitivity analyses and a meta-regression were performed to test the robustness of the results and to explore heterogeneity.

Results: The search identified 2931 studies, of which 29 were included in the meta-analysis, consisting of 130,862 patients. Intraoperative hypotension was associated with an increased risk of morbidity (odds ratio (OR) 2.08, 95 per cent confidence interval 1.56 to 2.77) and mortality (OR 1.94, 1.32 to 2.84). In the secondary analyses, intraoperative hypotension was associated with cardiac complications (OR 2.44, 1.52 to 3.93) and acute kidney injury (OR 2.69, 1.31 to 5.55). Overall heterogeneity was high, with an $I^2$ value of 88 per cent. When hypotension severity, outcome severity and study population variables were added to the meta-regression, heterogeneity was reduced to 50 per cent.

Conclusion: Intraoperative hypotension during non-cardiac surgery is associated with postoperative cardiac and renal morbidity, and mortality. A universally accepted standard definition of hypotension would facilitate further research into this topic.
Library databases were searched, with guidance of a clinical librarian, between January 1990 and August 2018. Search terms contained both Medical Subject Headings (MeSH) terms and free text to define patient population (type of surgery), event (IOH), and postoperative outcomes (morbidity and mortality). The complete search strategy is available in Appendix S1. Titles, abstracts and full texts were screened independently by two reviewers for relevance, with use of the review program Rayyan14. Disagreements were discussed with a third reviewer. Reference lists of the selected articles were examined for additional eligible articles. Studies were included when IOH was incorporated as a predictive variable for postoperative mortality or organ damage in adult patients undergoing elective non-cardiac surgery. Exclusion criteria were non-availability of full texts or language other than English. In case of non-availability, authors were not contacted. Reviews and case reports were excluded. Finally, studies describing IOH in combination with low bispectral index and low minimum alveolar concentration, the so-called ‘triple low states’15,16, were excluded from the review as the effect of hypotension alone could not be studied.

Outcomes
The prespecified primary outcomes were overall morbidity and mortality. Prespecified secondary outcome measures were cardiac adverse outcomes, AKI, neurological outcomes (stroke), delirium, surgical complications such as surgical-site infection or anastomotic leakage, and combined outcomes.

Data extraction
Data were extracted using predefined tables for data collection. Data extraction was done in duplicate. Extracted data consisted of study design, patient characteristics, methods, definition of IOH, type of BP measurement (non-invasive or arterial), and postoperative patient outcomes.

Quality assessment
Critical appraisal was based on the Newcastle–Ottawa Scale (NOS) for cohort studies to assess the quality of non-randomized studies17. The NOS is a grading system with scores given for selection (maximum 4 points), comparability (maximum 2 points) and outcome (maximum 3 points), with a highest possible score of 9. Studies with a NOS score greater than 3 were included in the quantitative meta-analysis, to reduce possible bias introduced by low-quality studies.

Meta-analysis
The included studies were analysed in an overall meta-analysis. For each study, only one definition of IOH and one outcome in terms of morbidity or mortality were used in the analysis. Considering that both the predictive variable IOH and the outcome measures morbidity and mortality are dichotomous, data were extracted into 2x2 tables. When studies presented results using multiple definitions of IOH or multiple outcome variables, one of each was selected to be incorporated in the analysis. The selection procedure for the definitions of IOH and outcome variables was predefined and agreed upon by all reviewers without knowledge of the potential effect of their selection on the results.

First, an overview of all IOH definitions and outcomes used in the various articles was done. If more than one definition of hypotension was present in the study, the definition that was used most frequently in all studies was chosen. To illustrate, a MAP of 60 mmHg was used more frequently to define hypotension than a MAP of 50 mmHg, so that when a study reported both, results for MAP of 60 mmHg were extracted.

Second, the same method was applied to select and extract outcome variables. To illustrate, MI was reported more frequently than myocardial injury. Therefore, if a study reported results for both myocardial injury and MI, the MI data were extracted.

Studies were categorized based on postoperative outcomes in the following groups: mortality, cardiac, renal, stroke, delirium, and any postsurgical complication. The postsurgical complication category included all studies that did not fit into the other categories, and included surgical-site infection, postsurgical complications graded according to the Clavien–Dindo classification18, anastomotic leakage, any postoperative complication and headache.

A random-effects meta-analysis was conducted, using inverse variance weighting to pool studies. Between-study variance ($\tau^2$) was estimated using the DerSimonian–Laird method. The percentage of the variability in effect estimates between studies that was due to heterogeneity rather than sampling error (chance) was expressed as the $I^2$ value. To assess possible publication bias, a funnel plot was constructed and inspected visually. Egger's test was performed to test for asymmetry of the funnel plot.

Subgroup analysis
Subgroup analysis, based on severity of hypotension, was performed to evaluate whether the definition of hypotension influenced the association found. Hypotension severity was ranked considering both duration and depth of hypotension. A panel of anaesthetists was used to rank the 29 included definitions of hypotension, starting from the most severe definition. The same rank could be used for different definitions if these definitions were thought to be of equal severity (Appendix S2). All questionnaires were collected, recalculated and averaged into a 1–9 scale. Based on this scale, studies were divided into three groups: mild, moderate, and severe hypotension.

Sensitivity analyses
Sensitivity analyses were performed to test the robustness of the association found, with the aim of assessing whether the decisions made during the review process affected the overall odds ratio (OR). Pooled ORs in the sensitivity analyses were inspected visually to assess whether they showed the same direction of association as the result of the primary meta-analysis. If the OR of a sensitivity analysis aligned with that found in the primary meta-analysis, the overall result and conclusions were not influenced by including or excluding particular studies and were thus regarded as robust. Predefined factors for sensitivity analyses were: outcome severity, generalizability of the study population, and methodological quality of the studies.

The outcome severity of each included study was scored based on the Clavien–Dindo classification18, which provides a validated grading system for the severity of postoperative complications. In this sensitivity analysis, the overall effect in studies with Clavien–Dindo grade IV and V was analysed.

To assess the influence of differences in study sample populations (generalizability) on the association between IOH and postoperative morbidity and mortality, the studies were divided based on the first question (S1) of the NOS scale: ‘Representativeness of the exposed cohort’. Studies that were classified as generalizable were selected for the sensitivity analysis.
To assess the influence of study quality on the association between IOH and postoperative morbidity and mortality, studies were divided based on low (NOS score 4–5) or high (NOS score 6–8) study quality. For this sensitivity analysis, high-quality studies were selected. To test ultimately the robustness of the meta-analysis, the studies initially excluded because of low study quality (NOS score below 4) were included in the final sensitivity analysis.

Meta-regression

A meta-regression was performed to account for the heterogeneity in the effect of IOH on postoperative mortality and morbidity. Before the analysis, it was hypothesized that hypotension severity, outcome severity and the generalizability of the patient population accounted for (part of) the heterogeneity. As subgroups based on outcome (primary analysis) and subgroups based on outcome severity have overlapping properties, only outcome severity was included as a factor in the meta-regression. Hypotension severity was assessed as described above. The amount of heterogeneity in the meta-regression was estimated using the maximum likelihood method.

Data analysis was performed using the statistical program R. The overall meta-analysis, sensitivity analyses, subgroup analysis and meta-regression were composed using the meta package in R.

Results

The initial search in MEDLINE, Embase and the Cochrane Library resulted in 2931 articles. Eight articles were found via citation tracking. Selection based on titles and abstracts resulted in 177 eligible articles. After screening of full texts, 133 articles were excluded. As a result, 44 articles were included in the qualitative synthesis (Table S1). Two articles used the same cohort of patients; both reported a (similar) secondary analysis of the VISION cohort. As this would introduce an overestimation of the weight of the VISION cohort, the article with the most severe outcome parameter was included. Fourteen articles were excluded based on low study quality based on the NOS scale.

Study characteristics

In total, 29 studies were included in the meta-analysis, a combined total of 130,862 patients. Mean(s.d.) age was 63(8) years, and 54% of studied patients were men. Of the 29 studies, 25 studied morbidity and four studied mortality. Among the included morbidity studies, one was a case-control study. This study used propensity score matching in a large cohort, resulting in a high study quality. Table S1 shows the quality of the studies included in the meta-analysis. The different definitions of IOH used are shown in Fig. S1.
Meta-analysis

The meta-analysis showed an overall significant association between IOH and postoperative morbidity and mortality (Fig. 2). Associations between IOH and postoperative complications were seen regarding cardiac outcomes (OR 2.44, 95 per cent confidence interval 1.52 to 3.99), AKI (OR 2.69, 1.31 to 5.55) and mortality (OR 1.94, 1.32 to 2.84). An association was found for IOH and the outcome subgroups ‘any postsurgical complication’ (OR 1.76, 1.04 to 2.98). There was no association between IOH and stroke (OR 0.81, 0.49 to 1.33) or delirium (OR 1.32, 0.47 to 3.71).

Heterogeneity

All studies assessed the effect of IOH on postoperative morbidity or mortality, but study designs varied. Heterogeneity between studies was high ($I^2=88$ per cent). Visual inspection of the funnel plot showed that, for both larger and smaller studies, negative as well as positive results were published. Egger’s test to test for asymmetry in the funnel plot showed that there was no indication of publication bias ($P=0.106$) (Fig. 3).

Subgroup analysis

Table S2 shows the hypotension severity ranking per study. Visual inspection showed that the ORs per subgroup increased with the severity of hypotension (Fig. S2). The subgroup of mild hypotension had an overall OR of 1.99 (95 per cent confidence interval 0.52 to 7.69), moderate hypotension had an overall OR of 1.59 (1.23 to 2.07), and severe hypotension had an OR of 2.62 (1.83 to 3.76).

Sensitivity analyses

All four sensitivity analyses indicated that the results of the meta-analysis were robust. Table S2 gives the Clavien–Dindo grade per study outcome. Fig. S3 shows that studies with a Clavien–Dindo grade III–V had a pooled association in the same direction as the overall pooled OR in the primary meta-analysis. Figs S4 and S5 show that the effect found in this meta-analysis remained when analysing solely studies classified as generalizable and when selecting only studies with the highest study quality.

Fig. S6 demonstrates that including studies with a very low study quality did not alter the overall results.

Meta-regression

Random-effects meta-regression revealed an association between the predefined factors and the amount of heterogeneity in the effect of IOH on postoperative morbidity and mortality. When the hypotension severity scale was included in the meta-regression, heterogeneity was reduced to 75 per cent ($P<0.001$). Fig. 4 depicts the association between severity of hypotension and outcome in a bubble plot. Adding the outcome severity scale as a second factor in this meta-regression reduced heterogeneity to 61 per cent ($P<0.001$). Finally, the generalizability of the studies was added to the meta-regression, further reducing the heterogeneity to 50 per cent (Appendix S3).

Discussion

IOH was associated with an increased risk of postoperative morbidity and mortality. This effect was most notable in studies with cardiac events, AKI and mortality as endpoints, indicating that these outcomes seem most susceptible to IOH.

These findings are in line with a recently published meta-analysis by Gu and colleagues, which showed that IOH alone (compared with the triple low state of IOH with low bispectral index and low minimum alveolar concentration) increased the risk of postoperative mortality and morbidity. However, these authors included only studies published to May 2016, excluding recently published articles. Moreover, they only extracted the results based on the most severe definition of hypotension, which might not provide the most clinically relevant effect estimation.

Wesselinck and co-workers performed a systematic review without meta-analysis, including all studies that reported on intraoperative outcome and hypotension, regardless of the possibility of extracting 2×2 tables. These authors reported that the association between IOH and outcome became stronger when the MAP was lower. However, various assumptions were made to translate the severity of different definitions of IOH, leading to debatable results.

Randomized trials are rare because it is difficult to maintain patients in predefined BP, and such trials are costly. Recently, the first RCT studying the effect in 292 patients of IOH on a composite postoperative outcome of systemic inflammatory response syndrome and dysfunction of at least one organ system was published. This trial evaluated the effect of an individualized BP strategy, aiming at a systolic BP within 10 per cent of the patient’s resting BP, compared with standard care. The authors reported a reduced risk of organ dysfunction with strict management of BP in patients undergoing abdominal surgery. In line with the results...
### Fig. 2 Forest plot of all included studies

A random-effects model was used for all meta-analyses. Odds ratios (ORs) are shown with 95 per cent confidence intervals. *Units for mean arterial pressure (MAP) are mmHg, MI, myocardial infarction, SBP, systolic BP, SSI, surgical-site infection.*

### Fig. 3 Funnel plot of all included studies

Egger’s test for funnel asymmetry: z = 1.62, P = 0.106.

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### Table: Pooled association for morbidity

| Reference | Cardiac subgroup | No hypotension | OR | OR | Weight (%) | Definition | Duration | Outcome event |
|-----------|-----------------|----------------|----|----|------------|------------|----------|---------------|
| Kheterpari | hy = 33 of 2854 | 47 of 4758 | 1.17 (0.75, 1.83) | 4.0 | MAP < 60 | n.a. | Combined cardiac |
| McLean House et al. | 163 of 38 024 | 29 of 6668 | 1.27 (0.85, 1.88) | 4.1 | MAP < 60 | n.a. | MI |
| Sassler et al. | 249 of 3404 | 418 of 6381 | 1.12 (0.95, 1.30) | 4.5 | SBP < 90 requiring therapy | n.a. | Combined cardiac |
| van Wassen et al. | 26 of 450 | 12 of 440 | 2.19 (1.09, 4.39) | 3.3 | MAP < 60 | 30 min | MI |
| Xu et al. | 66 of 405 | 63 of 967 | 2.43 (1.89, 3.51) | 4.2 | Combined 1 | 10 min | Combined cardiac |
| Sabaté et al. | 35 of 313 | 111 of 3974 | 3.36 (2.25, 5.01) | 4.1 | Combined 2 | 60 min | Combined cardiac |
| von Knorr et al. | 12 of 49 | 18 of 549 | 9.57 (4.29, 21.35) | 3.0 | SBP > 50% decrease | 10 min | MI |
| Hallqvist et al. | 7 of 34 | 7 of 266 | 11.38 (3.82, 33.91) | 2.3 | SBP > 50% decrease | 5 min | MI |
| Total | 45 of 583 | 24 of 981 | **2.44 (1.52, 3.93)** | 29.3 |

### Renal subgroup

| Reference | OR | OR | Weight (%) | Definition | Duration | Outcome event |
|-----------|----|----|------------|------------|----------|---------------|
| Hsieh et al. | **0.14** | 0.37 | 1 | 2.72 | 7 | 3.9 | 10 |
| Liu et al. | 61 | 54 | 62 | **2** | 4 | 1 | 2.72 | 7 | 3.9 | 10 |
| Total | 5223 | 2050 | **2.09 (1.31, 3.55)** | 23.5 |

### Stroke subgroup

| Reference | OR | OR | Weight (%) | Definition | Duration | Outcome event |
|-----------|----|----|------------|------------|----------|---------------|
| Hsieh et al. | 77 of 387 | 27 of 115 | 0.81 (0.49, 1.33) | 3.8 | **MAP < 70** | n.a. | Stroke |
| Total | 387 | 115 | 0.81 (0.49, 1.33) | 3.8 |

### Delirium subgroup

| Reference | OR | OR | Weight (%) | Definition | Duration | Outcome event |
|-----------|----|----|------------|------------|----------|---------------|
| Marcantonio et al. | 8 of 32 | 170 of 508 | **0.66 (0.29, 1.51)** | 2.9 | **MAP < 50** | n.a. | Delirium |
| Patti et al. | 27 of 352 | 90 of 989 | **0.83 (0.53, 1.30)** | 3.9 | Combined 4 | n.a. | Delirium |
| Total | 402 | 1579 | **1.32 (0.47, 3.71)** | 9.1 |

### Any postsurgical complication subgroup

| Reference | OR | OR | Weight (%) | Definition | Duration | Outcome event |
|-----------|----|----|------------|------------|----------|---------------|
| Balabazade | 130 of 801 | 258 of 1720 | **1.10 (0.87, 1.38)** | 4.4 | **MAP > 55** | n.a. | SSI |
| Sanzio Lastra et al. | 23 of 81 | 15 of 58 | **1.19 (0.56, 2.54)** | 3.1 | Combined surgical | n.a. | SSI |
| Matsouka et al. | 28 of 66 | 98 of 380 | **2.12 (1.24, 3.64)** | 3.7 | **MAP > 20% decrease** | n.a. | Headache |
| Post et al. | 13 of 205 | 8 of 80 | **2.64 (0.68, 11.97)** | 1.6 | **SBP > 40% decrease** | n.a. | Anastomotic leak |
| Ziser et al. | 117 of 261 | 105 of 472 | **2.64 (0.65, 3.94)** | 4.2 | **MAP > 20% decrease** | 10 min | Any complication |
| Total | 1414 | 2712 | **1.76 (1.04, 2.98)** | 17.0 |

### Mortality subgroup

| Reference | OR | OR | Weight (%) | Definition | Duration | Outcome event |
|-----------|----|----|------------|------------|----------|---------------|
| White et al. | 415 of 8578 | 94 of 2233 | **1.16 (0.92, 1.45)** | 4.4 | **MAP < 75** | n.a. | Mortality |
| Rothanov et al. | 133 of 4162 | 169 of 10025 | **2.02 (1.61, 2.55)** | 4.4 | **SBP < 90** | n.a. | Mortality |
| Monk et al. | 117 of 3407 | 217 of 15349 | **2.48 (1.97, 3.11)** | 4.4 | **MAP < 55** | 5 min | Mortality |
| Bijker et al. | 53 of 652 | 35 of 1053 | **2.57 (1.66, 3.99)** | 4.0 | **SBP < 80** | 1 min | Mortality |
| Total | 16 | 279 | **1.94 (1.32, 2.84)** | 17.3 |

### Overall

| OR | OR | Weight (%) | Definition | Duration | Outcome event |
|----|----|------------|------------|----------|---------------|
| 6 | 0 | **0.04 (0.92, 1.45)** | 4.4 | **MAP < 75** | n.a. | Mortality |
| 6 | 0 | **2.02 (1.61, 2.55)** | 4.4 | **SBP < 90** | n.a. | Mortality |
| 6 | 0 | **2.48 (1.97, 3.11)** | 4.4 | **MAP < 55** | 5 min | Mortality |
| 6 | 0 | **2.57 (1.66, 3.99)** | 4.0 | **SBP < 80** | 1 min | Mortality |
| Total | 6 | 0 | **2.04 (1.16, 2.57)** | 100.0% |

of the present meta-analysis, their results stress the importance of the prevention of hypotension during surgery.

IOH was not associated with stroke in this meta-analysis, although only one article reporting on stroke could be included, preventing definitive conclusions from being drawn. Furthermore, the *a priori* risk of postoperative stroke is extremely low, with a reported incidence of 0.1 per cent in non-cardiac, non-neurological surgery. As such, the study might have been underpowered.

IOH was also not associated with delirium. However, a recently published RCT found a significantly lower rate of altered consciousness level in the individualized BP group compared to standard care (5.4 per cent versus 15.9 per cent, *P* = 0.007).

This meta-analysis has provided an overview of the effect of IOH on multiple postoperative outcomes, aggregating all available evidence to date. Despite heterogeneity found between studies, the majority of studies show IOH to be associated with worse postoperative outcomes.
The debate about the importance of blood flow versus BP is long-lived. Both flow and pressure are required for adequate delivery of oxygen to tissues. BP is a parameter measured during long-lived. Both flow and pressure are required for adequate delivery of oxygen to tissues. BP is a parameter measured during long operations; blood flow, on the other hand, is rarely measured. Studies reporting on the effect of IOH on postoperative morbidity and mortality were included in the present review only if a 2 x 2 table could be constructed. This resulted in the exclusion of some large studies showing a positive association between IOH and outcomes. Inclusion of these studies would probably have led to a stronger association between IOH and postoperative outcomes.

Despite this, the inclusion criteria resulted in a relatively large number of included studies and an extensive overall study population. Unfortunately, heterogeneity was high. Studies differed with respect to the chosen definitions of IOH and the reported postoperative outcomes. Definitions of IOH were based mostly on either absolute thresholds, such as MAP and systolic BP, or a relative threshold (a decrease in BP relative to patients’ baseline BP). Different definitions of IOH may lead to different associations with adverse postoperative outcomes. Current definitions of IOH may lead to different associations with adverse postoperative outcomes. The intraoperative consensus statement advises that MAP be maintained above the 60–70 mmHg threshold. A universally accepted threshold would facilitate easier comparison between studies in the future.

The sensitivity analyses performed in this study indicated a robust pooled effect of IOH on postoperative outcomes and a large part of the heterogeneity found in the meta-analysis was explained by a combination of hypotension severity, outcome severity, and study population. Despite the fact that articles published in languages other than English were not included in this meta-analysis, the funnel plot and Egger’s test revealed no indication of publication bias.

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Supplementary material

Supplementary material is available at BJS Open online.

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