Systematic Review and Meta-Analysis

Hypotension prediction index for minimising intraoperative hypotension: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background and Aims: Reports on the utility of the hypotension prediction index (HPI) in reducing the occurrence of intraoperative hypotension are conflicting. Therefore, the aim of this systematic review and meta-analysis of randomised controlled trials (RCTs) was to evaluate the overall effect of using HPI on intraoperative hypotension outcomes of time-weighted average (TWA), area under the hypotension threshold (AUHT), incidence and duration of hypotension. **Methods:** We searched the electronic databases of PubMed, ProQuest and Scopus from inception till 30 October 2023. The search strategy was refined for each database. No time or language restrictions were applied. Only RCTs were included. The systematic review protocol is registered with PROSPERO (ID: CRD42023478150). Statistical analysis was performed using Review Manager Software. **Results:** Of 281 records, eight eligible RCTs (613 patients) were included. Significant differences were found between HPI and no HPI groups for the TWA of hypotension during surgery [mean difference (MD) = –0.19 mmHg, 95% confidence interval (95% CI): –0.31, –0.08, $P = 0.001$], AUHT [MD = –65.03 (mmHg × min), 95% CI: –105.47, –24.59, $P = 0.002$], incidence of hypotension (risk ratio = 0.83, 95% CI: 0.7, 0.99, $P = 0.04$), total hypotension duration (MD = –12.07 min, 95% CI: –17.49, –6.66, $P < 0.001$) and hypotension duration as a percentage of surgery time (MD = –6.30%, 95% CI: –10.23, –2.38, $P = 0.002$). **Conclusions:** Available evidence supports the role of HPI in minimising hypotension outcomes during surgery. The certainty of evidence is low to moderate for studied outcomes.

Keywords: Hypotension, hypotension prediction index, intraoperative, machine learning, metanalysis, monitoring, systematic review

INTRODUCTION

Intraoperative hypotension is a common but important complication during surgery. It is estimated that up to 87% of patients manifest with at least one episode of hypotension (mean arterial pressure less than 65 mmHg) during surgery.[1] Intraoperative hypotension can lead to various adverse consequences, such as delirium, acute kidney injury, myocardial ischaemia and stroke.[2,3] Preventing the occurrence and promptly correcting the intraoperative hypotension is critical to improving perioperative outcomes in surgical patients.

The conventional approach to intraoperative hypotension has been reactive, implying intervention is done after the hypotension has occurred. With advances in artificial intelligence and machine learning (AIML) in medical equipment, it is now possible to predict changes in physiological parameters before their occurrence.[4] Recently, Hatib *et al*.[5] developed

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an algorithm to predict hypotension minutes before blood pressure decreases. The hypotension prediction index (HPI) tool has been validated and has high sensitivity and specificity.[1,5] The Acumen HPI software (HemoSphere; Edwards Lifesciences, Irvine, CA, USA) has an algorithm developed using AIML from the arterial pressure waveform analysis. The HPI value ranges from 0 to 100, with higher values indicating an increased risk of developing hypotension in the near future.[1] The HemoSphere monitor displays the HPI value along with haemodynamic parameters of mean arterial pressure (MAP), systolic arterial pressure and diastolic arterial pressure, heart rate, stroke volume (SV), SV index, SV variation (SVV), pulse pressure variation (PPV), cardiac output and cardiac index. When the HPI is ≥85, visual and audible alarms alert about the impending hypotension. A secondary screen with a peak rate of arterial pressure (dP/dtmax) and dynamic arterial elastance (Eadyn = PPV/SVV) is then displayed, informing about the likely cause of hypotension. Since its commercial availability, HPI has been used in different surgical procedures to prevent intraoperative hypotension. Only a few randomised controlled trials (RCTs) have compared HPI with conventional blood pressure assessment for intraoperative hypotension management.[6-13] These trials are few, had small sample sizes to dictate a change in current clinical practice and reported conflicting findings, with some demonstrating benefit in hypotension reduction with HPI[6-10,12] while others did not.[11,13] A systematic review was necessary to provide a definitive answer and inform the overall evidence to guide anaesthesiologists regarding its utility.

This systematic review aimed to identify RCTs comparing intraoperative hypotension with HPI monitoring versus conventional monitoring and management of blood pressure in patients undergoing surgeries and inform the pooled estimates of effect for hypotension outcomes. Our primary objectives were to evaluate the time-weighted average (TWA) and area under the hypotension threshold (AUHT). Our secondary objective was to assess the incidence and duration of hypotension.

METHODS

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42023478150) and is being reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility criteria

We included RCTs comparing HPI with control for prediction, prevention and management of intraoperative hypotension during surgeries performed under general anaesthesia. No language or publication restrictions were applied during the initial stage. Only the trials published in English were planned to be included during the full-text review. We excluded non-RCTs, RCTs not involving the use of HPI during the intraoperative period and RCTs where hypotension outcome data would not be available.

Search strategy

We searched electronic PubMed, ProQuest and Scopus databases from their inception to 30 October 2023. The search strategy was refined for each database with the help of an experienced librarian. The search terms included the study population of patients undergoing surgery, the study intervention of HPI and a comparator other than HPI, and at least one hypotension outcome [Supplementary File 1].

Study selection

Two independent reviewers (TF and RKM) assessed the studies for selection in two stages (title and abstract screening and full-text review) after a calibration exercise before the start of the screening to ascertain consistency and accuracy in the selection of studies. Any disagreement was discussed for resolution, and if it was unresolved, the senior author (KS) settled it. Interobserver agreement was tested for full-text selection using the kappa statistic.

Data extraction

The same reviewers independently extracted the data from the included studies using a Microsoft Excel worksheet. The senior author (KS) prepared and provided an instruction sheet to help with data extraction. The extracted data included study details (author, year, journal, country, centres, sample size in each group and funding status), patient characteristics (age, gender and surgery details), interventions and comparators, definitions, details of outcomes assessed, and potential risk of bias (RoB). We contacted the study authors to obtain missing data or to clarify items related to the study.

RoB assessment

RoB of individual studies was assessed using the Cochrane RoB tool 2 for RCTs. Components of potential

bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result were obtained.[14] The RoB was classified as low, with some concerns, and high.

Outcome assessment

The primary outcomes of our study were intraoperative hypotension as TWA and AUHT. The AUHT (mmHg × minutes) is derived as follows: depth of hypotension below 65 mmHg of MAP × time in minutes spent below a MAP of 65 mmHg. The TWA (mmHg) is measured by calculating AUHT divided by the total duration of surgery (minutes). The secondary outcomes were the incidence and duration of hypotension, either absolute or as a percentage of total surgical duration.

Analysis and synthesis of results

The data was analysed using Review Manager Software (Rev Man version 5.4, The Cochrane Collaboration, 2020). A random effects model was used for analysis. This was done to capture uncertainty resulting from heterogeneity among studies. We calculated the risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes with their 95% confidence intervals (CIs). We used Cochran's Q test to estimate statistical heterogeneity and describe variability in individual effect estimates with I^2 statistics. If trials had more than two interventions, we compared data from only the HPI and no HPI groups. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach[15] with a summary of the findings table. We assessed for publication bias using a funnel plot and Eggar's test. A trial sequential analysis (TSA) was performed based on peer review suggestions, although it was not stated in the original review protocol.

RESULTS

We obtained 281 articles by searching three databases. Title and abstract screening was performed for 196 articles after removing 85 duplicate records. The full-text review was done for 11 articles, and after the exclusion of three articles,[16-18] eight articles were selected [Figure 1]. A substantial (91%) agreement was noted between the two reviewers for full-text review (kappa = 0.74).

Table 1 shows the characteristics of the included studies. One study had a third group (historical cohort), which was not used for analysis.[12] All studies used MAP of 65 mmHg as the threshold for defining intraoperative hypotension. All studies except one[8] had some conflict of interest for at least one author through funding of the study, individual payments or honorarium.

Three of the eight studies had concerns about the overall RoBs in at least two domains, while the RoB was low for five studies [Figure 2]. The RoB plots were created using the tool from https://mcguinlu.shinyapps.io/robvis/.[19]

Seven of the eight studies (n = 564) reported TWA of hypotension during surgery as one of the study outcomes.[6-11,13] TWA of hypotension was significantly lesser in the HPI group (n = 280) compared to the control group (n = 284) (MD = –0.19 mmHg, 95% CI: –0.31, –0.08, P = 0.001) [Figure 3a]. Six studies reported the AUHT using a MAP threshold of 65 mmHg (n = 524).[6-8,10-11,13] The AUHT was significantly lower in the HPI group (n = 260) when compared to the control group (n = 264) (MD = –65.03, 95% CI: –105.47, –24.59, P = 0.002) [Figure 3b]. Five studies reported the incidence of hypotension (n = 293).[6-8,10,13] The hypotension incidence was significantly lower in the HPI group (n = 147) compared to the control group (n = 146) (RR = 0.83, 95% CI: 0.7, 0.99, P = 0.040) [Figure 3c].

The total duration of hypotension was evaluated in eight studies (n = 613).[6-13] The hypotension duration was also significantly lower in the HPI group (n = 305) versus the control group (n = 308) (MD = –12.07 min, 95% CI: –17.49, –6.66, P < 0.001) [Figure 3d]. Six studies (n = 366) reported hypotension duration as a percentage of total surgical time.[6,7,9,10,12,13] The hypotension duration as a percentage of surgery time was significantly lesser in the HPI group (n = 183) compared to the control group (n = 183) (MD = –6.30%, 95% CI: –10.23, –2.38, P = 0.002) [Figure 3e].

The GRADE quality of evidence was assessed using GRADEpro GDT software[20] and is presented in Figure 4. The certainty of evidence on GRADE assessment was low for TWA of hypotension during surgery, total hypotension duration and AUHT. In contrast, it was moderate for hypotension duration as a percentage of total surgery duration and the incidence of hypotension. The low rating was mainly

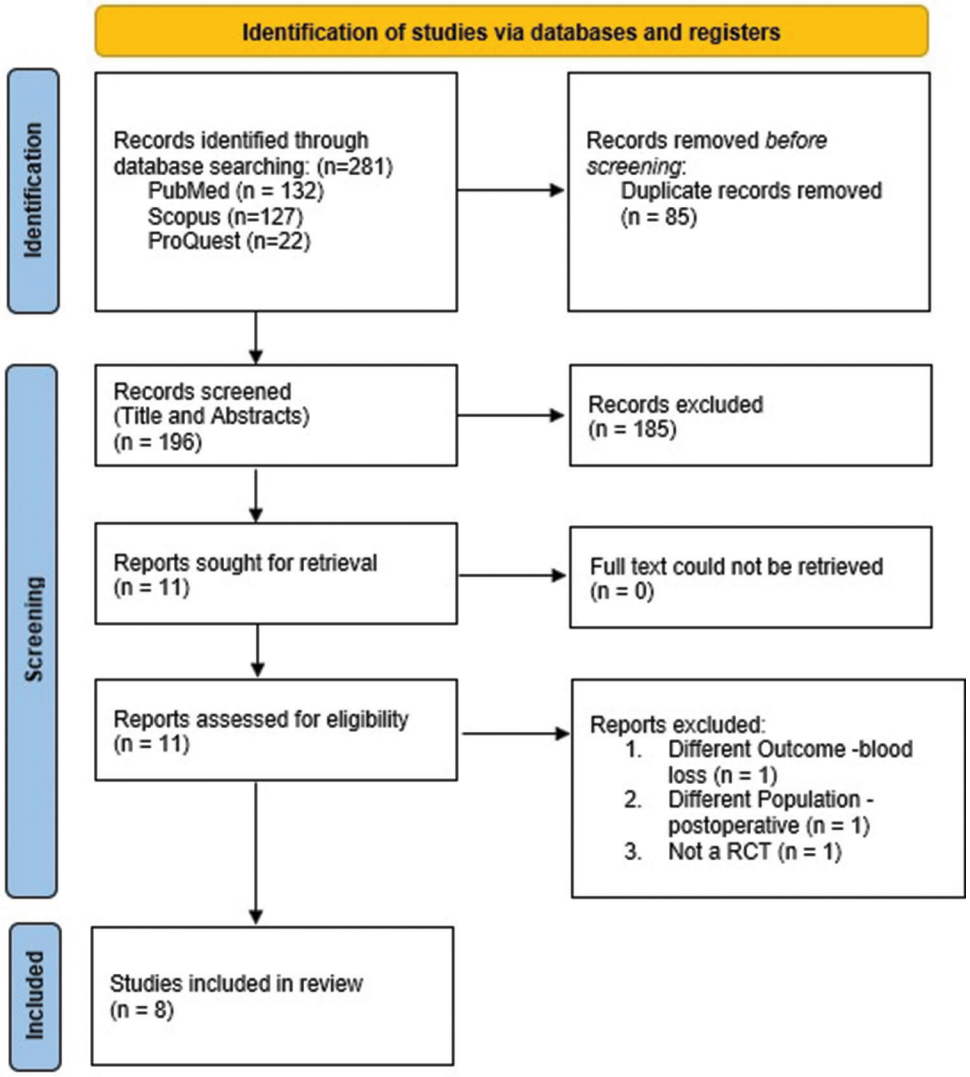

Figure 1: PRISMA flow diagram showing records obtained after a search of databases. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

due to inconsistency or imprecision in the outcome measures. A low GRADE level means the true effect may differ significantly from the estimated effect. In contrast, a moderate GRADE implies that the true effect is probably close to the estimated effect.

A significant publication bias was observed for the most commonly studied hypotension outcome in the included studies, the hypotension duration, as seen by an asymmetrical funnel plot and statistically significant Eggar's test ($P = 0.001$) [Figure 5].

TSA was performed for the primary outcome of TWA of hypotension with the package R version of Trial Sequential Analysis (version 0.2.2) to validate if the study sample size was appropriately powered to avoid random error. The heterogeneity correction was variance based, and a random effects model was used. The required information size was obtained using the conventional boundary and the O'Brien–Fleming continuous alpha spending boundary. The cumulative sequential Z score curve was constructed by calculating Z statistics from each study. As our sample size of 564 was less than the required sample size of 664, a false-positive, beneficial effect of HPI on intraoperative hypotension is possible. This finding suggests that future results may change with additional trials. However, the cumulative Z score crossed the trial sequential monitoring boundary for the benefit of HPI, increasing our confidence in our results [Supplementary File 2].

DISCUSSION

In this systematic review and meta-analysis of RCTs comparing HPI and no HPI to detect and manage intraoperative hypotension, the hypotension

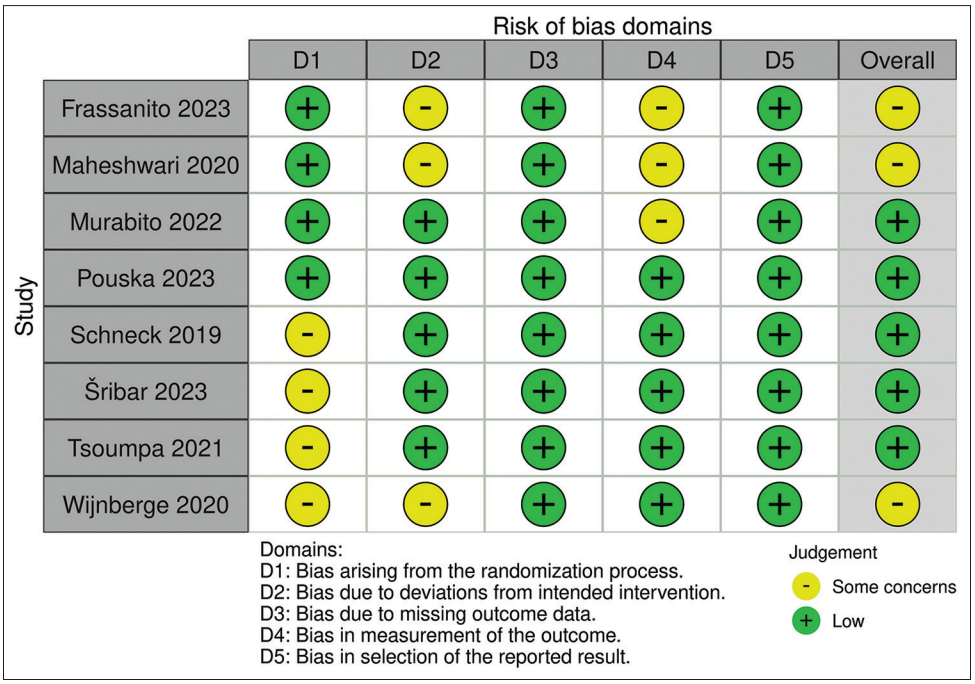

Figure 2: Potential risk of bias of included studies for various domains

Table 1: Characteristics of included studies

Study author, year, population	Surgery duration (min) [median (IQR) or mean (SD)]		Age (years) [Mean (SD)]		Male gender %		Intervention and comparator	Primary outcome	Funding and conflict of interests
	HPI	Control	HPI	Control	HPI	Control			
Schneck,[18] 2019, total hip arthroplasty	81 (62–90)	82 (68–100)	65 (11)	63 (12)	48%	54%	HPI and invasive blood pressure monitoring	Frequency and duration of hypotension	Edward Lifesciences
Wijnberge,[16] 2020, non-cardiac surgery	256 (194–425)	259 (223–442)	67 (9)	62 (9)	68%	45%	Early warning system and invasive blood pressure monitoring	TWA of hypotension during surgery	Edward Lifesciences
Maheshwari,[11] 2020, non-cardiac surgery	342 (174)	372 (156)	67 (10)	66 (10)	58%	65%	HPI guided and unguided	TWA of hypotension during surgery	Edward Lifesciences
Tsoumpa,[10] 2021, non-cardiac surgery	207 (150–255)	207 (150–332)	66 (12)	67 (14)	53%	58%	HPI guided and unguided	TWA of hypotension during surgery	Edward Lifesciences- free software and fees for an author
Murabito,[9] 2022, laparotomy surgery	207 (64)	237 (121)	NA	NA	50%	60%	Early warning system and invasive blood pressure monitoring	Incidence of hypotension	Edward Lifesciences and University of Catania
Frassanito,[7] 2023, gynaecologic oncosurgery	NA	NA	58 (21)	59 (15)	NA	NA	HPI and EV1000	TWA of hypotension during surgery	Edwards Lifesciences- two authors received an honorarium
Šribar,[8] 2023, thoracic surgery	165 (123–228)	180 (150–185)	64 (6)	67 (8)	58%	47%	AcumenIQ and Flowtrac	TWA of hypotension during surgery	Nil
Pouska,[13] 2023, brain tumour surgery	258 (216–365)	247 (232–319)	54 (13)	54 (14)	50%	45%	HPI and invasive blood pressure monitoring	Incidence of hypotension	Edward Lifesciences- one author received fees, Ministry of Health of Czech Republic

HPI=Hypotension prediction index, IQR=Interquartile range, NA=Not available, SD=Standard deviation, TWA=Time-weighted average

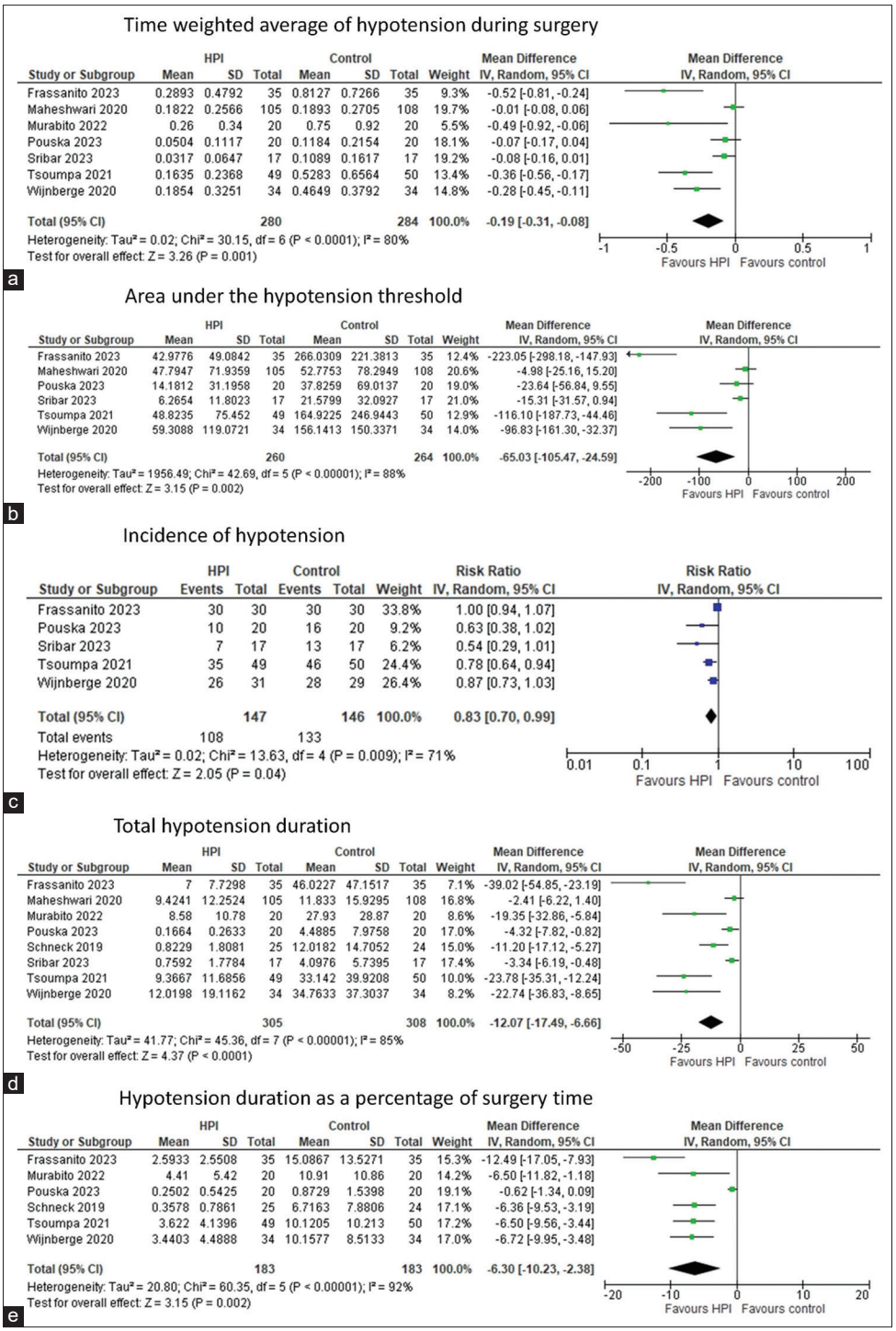

Figure 3: Time-weighted average of (a) hypotension during surgery, (b) hypotension duration as a percentage of surgery time, (c) hypotension duration, (d) area under the hypotension threshold and (e) incidence of hypotension

outcomes (TWA of hypotension, hypotension duration as the absolute value and as a percentage of surgery duration, AUHT and incidence of hypotension) were significantly in favour of HPI. However, TSA revealed the need for further RCTs to provide a more decisive answer regarding the impact of HPI on minimising intraoperative hypotension.

Most patients undergoing surgery manifest with intraoperative hypotension, and aetiologies vary in different individuals. However, patients are commonly monitored for hypotension using non-invasive or invasive blood pressure monitoring to guide hypotension management, which may not be adequate. Advanced haemodynamic parameters (SVV,

HPI compared to no HPI for minimizing intraoperative hypotension

Patient or population: patients undergoing surgery
Setting: intraoperative period
Intervention: HPI
Comparison: no HPI

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no HPI	Risk difference with HPI
TWA of hypotension during surgery (TWA)	564 (7 RCTs)	⨁⨁◯◯ Low[a,b]	-		MD **0.19 lower** (0.31 lower to 0.08 lower)
Hypotension duration as a percentage of surgery time (Hypotension%)	366 (6 RCTs)	⨁⨁⨁◯ Moderate[a,b]	-		MD **6.3 lower** (10.23 lower to 2.38 lower)
Hypotension duration	613 (8 RCTs)	⨁⨁◯◯ Low[a,b]	-		MD **12.07 lower** (17.49 lower to 6.66 lower)
Area under the hypotension threshold (AUC-HT)	524 (6 RCTs)	⨁⨁◯◯ Low[a,b]	-		MD **65.03 lower** (105.47 lower to 24.59 lower)
Incidence of hypotension (Incidence)	293 (5 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.83** (0.70 to 0.99)	911 per 1,000	**155 fewer per 1,000** (273 fewer to 9 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. variation in effect
b. Confidence intervals cross the clinical decision threshold

Figure 4: GRADE certainty of evidence for five study outcomes. GRADE = Grading of Recommendations, Assessment, Development, and Evaluations

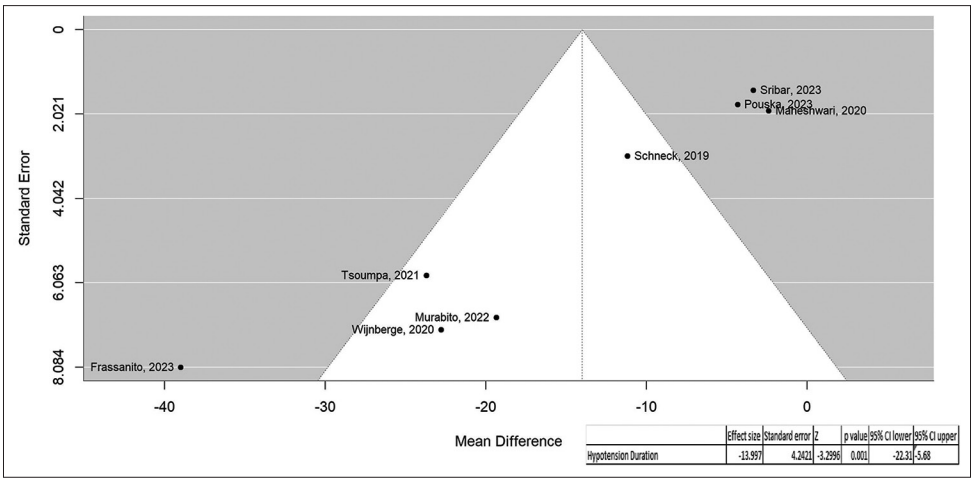

Figure 5: Funnel plot for intraoperative hypotension duration

CI, systemic vascular resistance, etc.) are used in select populations vulnerable to hypotension in the intraoperative period or patients with preexisting cardiovascular pathologies.[21] Even though these advanced parameters change only after hypotension, they help guide appropriate intervention. With the recent availability of machine learning algorithms, as in HPI, it is now possible to predict the subsequent occurrence of hypotension, which not only provides the time for implementing the intervention but also guides therapeutic intervention depending on the probable cause, thus reducing the incidence and severity of intraoperative hypotension.

Facilitating individualised blood pressure management using HPI can help in anticipating and minimising intraoperative hypotension and reducing postoperative organ dysfunction.[22] While few RCTs demonstrated the benefits of HPI in preventing hypotension,[6-10,12] others did not.[11,13] The differences could be due to the trial designs, study populations, HPI index algorithm issues and the response of the anaesthesiologists to

the alerts and time taken to implement the appropriate interventions. A systematic review can overcome the limitations of individual RCTs and provide a higher level of evidence for clinicians to implement care decisions in their practice.[23]

There are some important limitations. First, we observed high heterogeneity among the included studies with significant between-study variability. Hence, a random effects model was used for meta-analysis. Second, we also noted a significant publication bias for the hypotension outcome we studied. Third, most of the selected studies were funded by the HPI software company, exposing them to potential bias. Fourth, the trials included were single-institute studies with small sample sizes. Fifth, all studies used a fixed definition of intraoperative hypotension (MAP < 65 mmHg). However, the definition of hypotension and its intervention are dynamic in practice and are often determined by patient characteristics and end-organ perfusion requirements. However, the threshold of MAP of 65 mmHg is based on consensus guidelines recommending a MAP value of 60–70 mmHg during the surgery.[24] The HPI tool is also not without limitations. The early warning signal is fixed as it does not include dynamic learning evolving during surgery and anaesthesia and hence does not absolutely prevent hypotension occurrence. Moreover, the availability and cost of this tool and the use of the obtained information to intervene promptly and correctly are specific limitations of HPI.

CONCLUSION

Our systematic review demonstrates that HPI reduces adverse intraoperative hypotension outcomes in patients undergoing various non-cardiac surgeries using the machine learning-based hypotension prediction algorithm. However, the certainty of evidence on GRADE assessment is low to moderate for the outcomes studied, and TSA suggests the requirement of more RCTs to confirm the benefits of HPI in reducing intraoperative hypotension.

Study data availability

The data collected for this systematic review and meta-analysis may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared upon request.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY FILE 1

Supplementary data: Search strategy

PubMed

((hypotension prediction index) OR (early warning system)) AND (intraoperative hypotension)

Scopus

hypotension AND prediction AND index OR early AND warning AND system AND intraoperative AND hypotension AND (LIMIT-TO (SUBJAREA, "MEDI")) AND (LIMIT-TO (DOCTYPE, "ar"))

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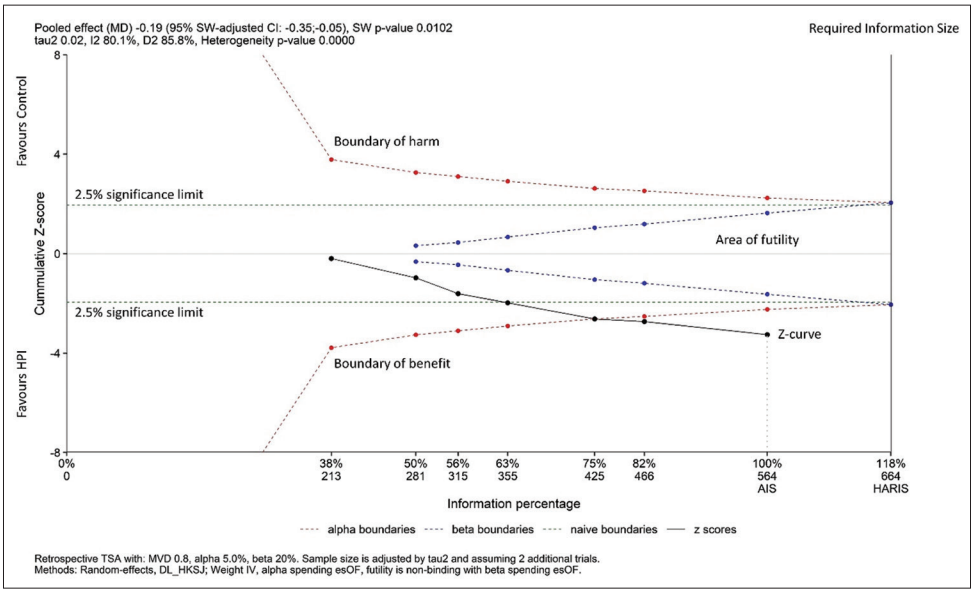
abstract (((Hypotension prediction Index) OR (early warning system)) AND (intraoperative hypotension))

SUPPLEMENTARY FILE 2

R version Trial sequential analysis (TSA) for a time-weighted average of hypotension (primary outcome). The lower half of the graph below the zero axis represents the area of advantage for the HPI group, and the upper half represents the advantage area for the control group. The solid black dots indicate the cumulative z score with the addition of each of the seven trials in chronological order. The green dotted lines on the Y-axis represent the conventional model boundaries (naïve boundaries) for TSA with an alpha error of 5%. The red dotted lines represent the alpha-spending boundary (alpha boundaries) with upper O'Brien Fleming, alpha of 5% and low risk of bias. The actual information size (AIS) is 564, and the heterogeneity adjusted required information size (HARIS) for this model is 664.



Supplementary File 2: Trial Sequential Analysis