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Master thesis | Original study

Automatic closed-loop anesthesia: a scoping review

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Abstract

Background: **The field of anesthesia has historically relied on manual administration, requiring anesthesiolgists to adjust dosages based on patient and surgical needs. With technological advancements, closed-loop systems have emerged to automate anesthesia administration, enhancing dosing accuracy, reducing workload, and improving patient safety. This scoping review investigates the application of closed-loop anesthesia across various clinical contexts, such as hypnosis, hemodynamic management, muscle relaxation, ventilation, and glucose control.**

The review employs a comprehensive methodology, adhering to contemporary scoping review guidelines. A thorough search of databases and grey literature yields a diverse collection of studies. A total of 327 articles are assessed, with 121 articles meeting inclusion criteria. Various closed-loop controllers are employed, of which Proportional Integral Derivative (PID) is the most frequent.

In the context of hypnosis, closed-loop systems demonstrate improved time on target, performance, and reduced drug consumption. Similarly, in hemodynamics, closed-loop administration of fluids and vasopressors results in optimized blood pressure and heart rate control. Muscle relaxation studies highlight the role of closed-loop controllers in maintaining appropriate levels of neuromuscular blockade.

While closed-loop systems show promise in improving anesthesia delivery, manual intervention remains necessary due to the dynamic nature of surgical settings. The review underscores the potential benefits of closed-loop anesthesia, including enhanced safety, reduced workload, and improved patient outcomes. However, the heterogeneity of study designs and applications necessitates cautious interpretation of findings. As technology continues to advance, refined closed-loop systems hold the potential to play an increasingly significant role in routine clinical anesthesia practice.

Keywords: **Anesthesia, Anesthesia, General, Anesthesia, Intravenous, Neuro-muscular Blockade, Hypotension, Controlled.**

Introduction

The administration of anesthesia products has historically relied on manual interventions, with anesthesiologists exercising their expertise to meticulously titrate the required dosage based on patient-specific factors and the nature of the surgical procedure. However, as technology continues to advance, there has emerged the capacity to automate certain aspects of anesthesia administration. This automation not only enhances dosing precision and monitoring but also alleviates the workload burden on anesthesiologists. Furthermore, it contributes to heightened safety levels by reducing errors and improving reproducibility[1,2].

In recent years, there has been a growing interest in the full automation of anesthesia administration through closed-loop systems. These systems entrust algorithms with the responsibility of determining the appropriate drug dosages based on specific measured parameters. This development has ushered in a wide array of potential applications, spanning from the induction of hypnosis to the management of blood pressure and muscle relaxation, each necessitating distinct setups and algorithms. In this comprehensive

scoping review, our aim is to provide an extensive overview of the discoveries made in recent years, the frequently utilized devices, and the associated algorithms in the realm of closed-loop anesthesia administration.

Methods

Before commencing our review, we formulated a protocol to guide our approach, which was uploaded on July 4, 2022, and is accessible at https://osf.io/qv7ux[3]. This protocol, along with the ensuing scoping review, adheres rigorously to the latest guidelines governing scoping reviews, including those delineated in the PRISMA-SCR statement. A detailed PRISMA checklist is available in Appendix I[4-8]. Our inclusion criteria encompassed articles focused on closed-loop systems within the practice of anesthesia, particularly those comparing them to human operators. This encompassed a broad spectrum, including but not limited to depth of sedation, neuromuscular relaxation, and hemodynamic support. To maintain our focus exclusively on anesthesia practice, we excluded papers centered on other medical domains, such as intensive care. Additionally, theoretical or virtual studies and those confined to animal testing were excluded to ensure a concentration on the practical facets of closed-loop anesthesia administration. Furthermore, we excluded articles lacking free full-text access in either English or Dutch, accessible through the KU Leuven or UZ Leuven libraries. Replies to prior articles were also omitted. Following the completion of our search, we opted to exclude papers published prior to the year 2000, as their contributions were deemed limited given the advancements in pharmacokinetic models and computational capabilities.

Our search for potential articles was conducted across several databases, including Medline (Pubmed), Embase, and Cochrane, with the final search executed on July 17, 2022. Grey literature was explored on clinicaltrials.gov and ICTRP. Our search strategy was informed by the guidance

Appendix I

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	3
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	3
Information sources[1]	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	3
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	3
Selection of sources of evidence[2]	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	4
Data charting process[3]	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	4
Critical appraisal of individual sources of evidence[4]	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	nil (4)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	4
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	4
Characteristics of sources evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	4
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	nil (4)
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	4
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives	6
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	7
Limitations	20	Discuss the limitations of the scoping review process.	24
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	25
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	26

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

[1]Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

[2]A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote). [3]The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

[4]The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

of the 2Bergen University Hospitals of Leuven Libraries and underwent refinement through discussion. The search string encompassed Mesh terms ("anesthesia", "closed loop") and title and abstract searches (("closed circuit" OR "closed loop") AND ("anesthesia*" OR "anaesthesia*" OR "anesthestic*" OR "anaesthetic*" OR "hypnotic*")). A total of 2805 articles were identified, subsequently deduplicated in EndNote to yield 1917 articles in total[9]. The final search strategy is included in Appendix III.

Following the deduplication process, all articles were imported into Rayyan.ai, which served as the platform for two independent reviewers to assess inclusion or exclusion based on predefined criteria[10]. Articles were blinded and individually categorized as "included," "maybe," or "excluded." If an article was flagged as "included" by at least one reviewer without a corresponding "excluded" flag, it was ultimately included. Conversely, if an article was flagged as both "included" and "excluded," efforts were made to achieve consensus between the reviewers. If consensus remained elusive, an independent third party was consulted. A flow chart detailing this selection process is provided in Figure 1.

Subsequent to the identification of all articles to be included, we embarked on the data charting process. To determine the variables worthy of extraction, we conducted an initial survey of several articles to gain insight into commonly reported outcomes and relevant variables. A solitary reviewer employed Microsoft Excel to develop an initial framework, drawing inspiration from a template provided by the Joanna Briggs Institute, which was subsequently adapted and iteratively refined[7]. A comprehensive version of the data charting file can be found in Appendix II.

The data items selected for inclusion spanned article characteristics (e.g., author, publication year, research type), surgery characteristics (e.g., surgical type), patient characteristics (e.g., quantity, age,

Appendix III: Search strategy.

On the 17th July 2022 the following databases were searched with the search terms just below in italic:

PubMed - MEDLINE
"Anesthesia, Closed-Circuit"[Mesh] OR (("closed circuit" [tiab] OR "closed loop"[tiab]) AND ("anesthesia"[tiab] OR "anaesthesia*"[tiab] OR "anesthetic*"[tiab] OR "anaesthetic*"[tiab] OR "hypnotic*"[tiab]))*

Embase
'closed loop system'/exp OR 'closed loop control'/exp OR 'closed loop control system'/exp OR (('closed circuit':ti,ab,kw OR 'closed loop':ti,ab,kw) AND ('anesthesia':ti,ab,kw OR 'anaesthesia*':ti,ab,kw OR 'anesthetic*':ti,ab,kw OR 'anaesthetic*':ti,ab,kw OR 'hypnotic*':ti,ab,kw))*

Cochrane
("closed loop control systems" OR "closed loop control system" OR "closed loop control" OR "closed loop" OR "closed-loop control systems" OR "closed-loop control system" OR "closed-loop control" OR "closed-loop") AND (Anesthesia OR Anaesthesia OR Anesthetic OR Hypnotic)

Clinicaltrials.gov
("closed loop control systems" OR "closed loop control system" OR "closed loop control" OR "closed loop") AND (Anesthesia OR Anaesthesia OR Anesthetic OR Hypnotic)

ICTRP
("closed loop control systems" OR "closed loop control system" OR "closed loop control" OR "closed loop" OR "closed-loop control systems" OR "closed-loop control system" OR "closed-loop control" OR "closed-loop") AND (Anesthesia OR Anaesthesia OR Anesthetic OR Hypnotic)

Since we only decided to exclude articles written before the year 2000 after the final search, no filter had been applied yet.

ASA classification), anesthesia characteristics (e.g., general anesthesia with or without locoregional techniques, drug selection, drug dosage with baseline administration), closed-loop characteristics (e.g., controller type, controlled variable, performance), and intervention characteristics (e.g., control group size, comparison, blinding).

Critical appraisal of the selected articles was not undertaken. To synthesize the results, we grouped papers by their primary application (e.g., hypnosis and sedation, hemodynamics, muscle relaxation). If necessary, we further subdivided these groups to maintain clarity and structure. The most significant findings were summarized in Tables (I, II, III and IV) and presented narratively. Following the completion of the full manuscript, we opted to post-process the text using ChatGPT to enhance its readability and language[11]. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Results

1. General principles

1.1. Definitions

A closed-loop system may be defined as a system in which a controller autonomously determines the new input based on the registered output[12]. In contrast, an open-loop system operates without the output influencing the input, necessitating manual adjustments[12]. Many anesthesiologists are already acquainted with Target Controlled Infusion (TCI) systems, which represent a prime example of open-loop systems[13].

1.2. Requirements

For a closed-loop system to attain success, it must surmount specific challenges. A pertinent set point is imperative, along with mechanisms to mitigate artifacts[12]. Absent these prerequisites, the patient could remain excessively alert, as the controller strives toward an irrelevant target, or external interferences could disrupt medication administration, potentially precipitating hazardous situations.

Ideally, input should involve a drug characterized by rapid response and short half-life, as this minimizes delays and enhances safety[12,13]. A highly precise mathematical model is requisite for a controller to be clinically effective, thereby bolstering robustness, mitigating uncertainty, and reducing variability, which collectively contribute to safer control across diverse scenarios[16,17]. In the context of this study, an effective pharmacokinetic-pharmacodynamic (PK-PD) model tailored to individual patients, accommodating uncertainty, is pivotal[16,17]. The establishment of rigorous boundaries is paramount to curb critical overdosing and underdosing[16].

1.3. Types of controllers

Proportional Integral Derivative Control (PID)

PID controllers, renowned for their simplicity and frequent application (e.g., cruise control in automobiles), calculate output based on present errors (proportional), past errors (integral), and predictions of future errors (derivative)[13].

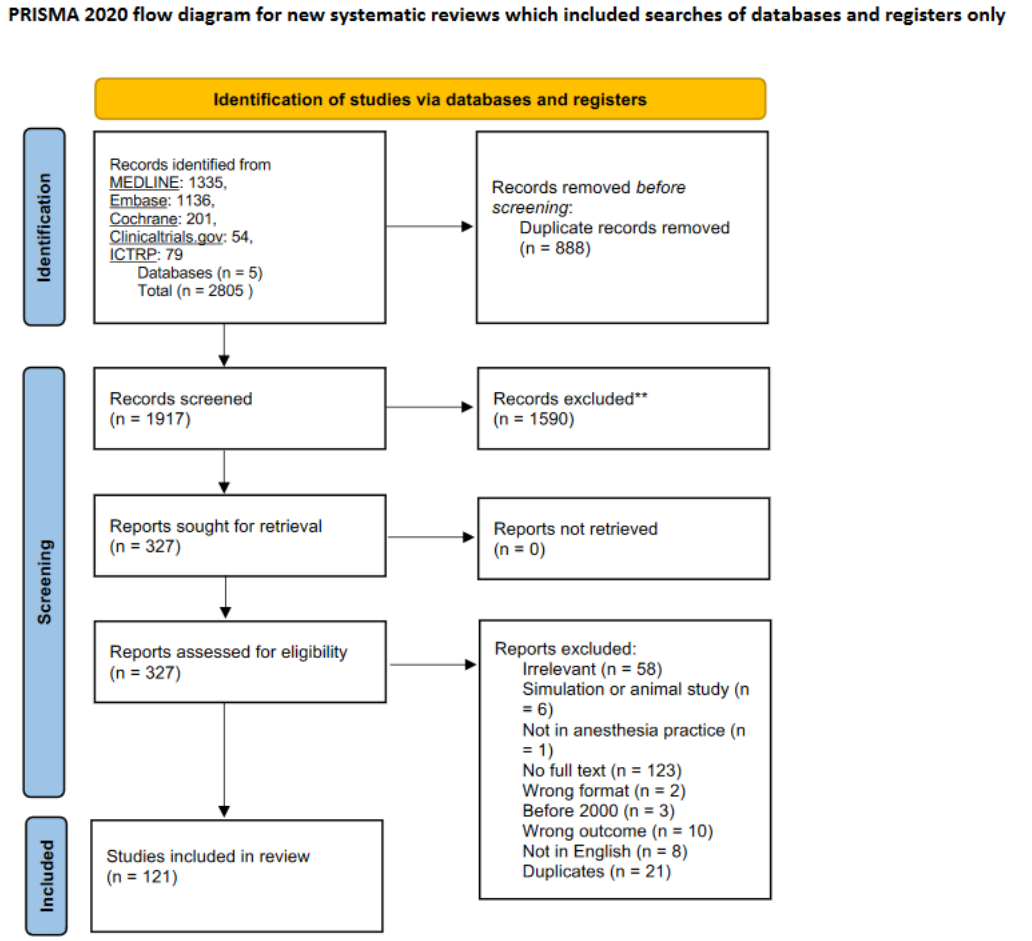

Fig. 1 — PRISMA flow chart.

Model Predictive control (MPC)

MPC necessitates the provisioning of a system model, which is subsequently employed to predict its future trajectory based on preceding inputs and outputs[16].

Adaptive control

Adaptive control is indispensable in systems characterized by significant time-varying behavior, such as substantial blood loss, which can alter the effects of drug[16]. This approach mandates the formulation of a robust system model and is inherently more complex[16].

2. Clinical applications

The findings have been organized in accordance with their application domains (Hypnosis and sedation, Hemodynamics, Relaxation, Respiratory, and Others) and are presented in their respective tables. Certain studies are duplicated across multiple tables, owing to their examination of various topics. To maintain the tables' clarity, solely significant results are recorded, while certain details are omitted. Comprehensive details can be found in a separate Results Excel file, available upon request.

2.1. Hypnosis

Our examination identified 66 articles elucidating closed-loop anesthesia or sedation. Of these, 3 constitute meta-analyses, and 11 are randomized controlled trials (RCTs). The meta-analyses report superior performance, prolonged time on target, and diminished Propofol consumption[18,19,20].

Among these articles, 5 employed inhalation anesthetics as hypnotic agents, while others utilized Propofol, often in conjunction with Remifentanil, in closed-loop systems (24) or incorporated locoregional techniques (6). The majority of articles

relied on a PID controller, with BIS as the primary output (55), and the chief outcomes encompassed time on target, satisfactory anesthesia, and controller performance. Notably, many of the earlier studies did not incorporate a control group (18) and frequently featured smaller sample sizes (1-34 patients).

2.2. Hemodynamics

Among the 19 articles scrutinizing hemodynamic management, 1 had already been addressed in the aforementioned meta-analysis, 7 pertained to fluid administration, and 11 focused on vasopressor administration. The meta-analysis exclusively evaluated anesthetic administration, revealing an extended period of heart rate and blood pressure maintenance on target[18].

The studies giving fluids most often gave boluses of 100ml, monitoring the difference it generated in SVV (Stroke Volume Variation) and MAP (Mean Arterial Pressure), which resulted in a lower net fluid balance. When administering vasopressors, the drugs most often used were Noradrenaline and Phenylephrine, which resulted in less hypotension, also lasting shorter. Similar to the hypnosis studies, the older studies were often without control group (5) and with smaller sample sizes (1-55).

2.3. Relaxation

Ten articles were identified pertaining to relaxation monitoring, with five of these also featuring in other sections. All but one study employed the Train of Four (TOF) monitoring technique, administering a variety of muscle relaxants, with Rocuronium being the most prevalent. Most studies reported comparable results regarding consumption and relaxation levels.

2.4. Other

This category incorporated two studies addressing respiratory interventions, two focused on glucose management, and one broad meta-analysis encompassing multiple applications, some of which were also addressed elsewhere. These studies reported favorable outcomes, with closed-loop techniques effectively managing ventilation, adapting to perioperative changes, and maintaining end-tidal CO2 within target ranges. Studies examining glucose management documented increased insulin administration accompanied by improved overall performance. The overarching meta-analysis reported extended periods on target, along with reduced instances of undershooting and overshooting, for the closed-loop groups[21].

Discussion

Summary of evidence

In this comprehensive scoping review, we endeavored to investigate the current utilization of closed-loop drug administration in anesthesia practice. We executed this endeavor by scrutinizing articles discussing the application of closed-loop systems in human patients, with a deliberate exclusion of those unrelated to the perioperative setting. Given the extensive scope of closed-loop systems, encompassing diverse clinical applications such as hemodynamics and sedation, direct comparison of results proves challenging, with no definitive superiority established among techniques.

Hypnosis and sedation

Upon examination of hypnosis studies, a notable degree of heterogeneity becomes evident. Diverse articles incorporated locoregional techniques, Remifentanil as an adjuvant, and inhalation anesthetics as hypnotic agents, while others used Propofol. Variability extended to drug selection, study design, and the presence or absence of control groups.

The utilization of BIS as a common output measure, often with PID controllers or self-developed systems, was consistent across studies. Surgical contexts ranged widely, from endoscopic procedures to laparoscopic and cardiac surgeries. The importance of hypnosis during a procedure diminishes when adequate analgesia can be provided, such as through locoregional techniques. When Remifentanil and Propofol are co-administered, their synergistic effects augment potency. In addition, not all studies used a control group and sometimes the control group was not allowed to use TCI.

In general, the closed-loop groups, seemed to outperform the manual groups in several fields, like time on target, overall performance and time to awakening. One reason to explain this would be the possibility of the controller to constantly evaluate its dose and its given, updating in real time, focusing on sole task. The anesthesiologist in contrast, has several other parameters to look after, sometimes even different operating theaters all together, in addition to having to do administrative work, and supervise the controller for malfunction. This limits the possible brain capacity that can be used to constantly monitor the depth of sedation. Induction time did not seem to fully favor one or either group. Maybe, because the differences in wake-up time were rather small. Several papers did note the need for manual intervention, however, highlighting the need for constant supervision

of the closed-loop device. This in part because the controller cannot predict certain changes in surgery, like for example increased stimulus, blood loss or clamping of arteries, forcing it to take a reflexive approach.

Hemodynamics

We could identify 2 big groups in the hemodynamic management: the administration of fluids and the administration of vasopressors, with some studies using both. The studies tested a variety of surgical settings, of which abdominal surgery was the most frequent for the fluid administration, and elective cesareans being the most popular for vasopressor administration.

The studies looking at fluid administration almost exclusively used a self-developed controller, using several cardiovascular parameters like heart rate, (non-)invasive blood pressure, stroke volume variation and Clearsight to guide the fluid administration. They mainly reported the time of fluid dependency and total fluid balance, favoring the closed-loop group which had shorter times of fluid dependency and lower total fluid balances. It should be noted that these seemingly conflicting results originate from different studies, making some studies report lower fluid balances, and others less time of fluid dependency. This could possibly be explained by the subjective nature of fluid administration, resulting in more liberal approaches in certain studies and more restrictive approaches in others.

When investigating the studies balancing vasopressors, we again note that self-developed controllers are the most frequent, followed by PID controllers. Similarly, to the fluid studies, outputs measured consisted of (non-)invasive blood pressure, heart rate, stroke volume variation and cardiac index. The 3 RCT's noted an improved controller performance with less hypotension and more time on target. The manual control groups, however, did not always administer medication in exactly the same way, possibly accounting for this difference.

The other studies included a variety of situations, of which elective cesareans were by far the most frequent. They reported similar results, with better times on target and less hypotension when compared to manual administration. Here too, we note that sometimes these manual groups had protocols which forced other doses. Additionally, manual overrides were sometimes reported.

Relaxation

The PID and self-developed controller were the most popular and all but one study had the TOF as output. The 2 RCT's both administered Rocuronium, comparing it to manual administration, reporting similar results.

In the other studies Rocuronium was the most frequent, but also Mivacurium, Cisatracurium and Atracurium were investigated. The target varied between 2 out of 4 responses and 10%. The studies without control group reported satisfactory conditions and only needing intervention in one study for 4 patients.

When compared to manual administration most results were similar, one study reported faster return to baseline with lower variability.

Other

The 2 studies controlling the ventilation of patients used a PID controller, measuring the EtCO2 and other respiratory parameters. They were able to attain satisfactory clinical results, needing intervention in 1 patient. When compared to manual administration, they found better results with longer time on target and less overshoot. Possibly, this difference can be explained by the protocol to which the manual administration had to adhere; they had less flexibility in their treatment using a fixed tidal volume and PEEP, where the closed-loop protocol had more freedom.

When comparing the glucose management and Insulin administration, the blood glucose levels were used as output. This resulted in higher Insulin administered with lower standard deviation and lower creatinine levels.

The one META analysis investigating a variety of clinical applications of closed-loop in anesthesia reported a better performance of the closed-loop groups in sedation, Insulin administration, ventilation and administration of vasopressors, in time on target, undershooting and overshooting.

Cost-effectiveness

While direct investigations into cost-effectiveness were not found, a plausible deduction suggests that a reduction in the total amount of drugs administered could lead to cost savings. However, this hinges on whether the potential drug savings outweigh the costs associated with the acquisition and maintenance of the closed-loop device and controller, most of which are not currently commercially available yet. Moreover, if favorable clinical outcomes contribute to reducing patient morbidity, total hospital stay, and complication rates, the overall cost may decrease. Unfortunately, few studies reported on the length of stay, both in the recovery room and the hospital, and the available data yielded nonsignificant results. Additionally, longer-term follow-up assessments

were infrequently conducted, making predictions about cost reduction challenging. Subsequently, further research is warranted before widespread adoption of these advanced devices in most hospital settings.

Limitations

Several limitations should be acknowledged. The substantial variability across studies, including differences in study design, control groups, controller types, and clinical contexts, complicates direct comparisons and the establishment of definitive conclusions regarding the superiority of closed-loop systems over manual administration. Additionally, the majority of studies exhibited smaller sample sizes, potentially limiting the generalizability of findings. The scarcity of studies addressing muscle relaxation further highlights the need for additional research in this area. Finally, while efforts were made to comprehensively search the literature, the exclusion of studies not available in English or Dutch and those published before 2000 may have resulted in the omission of relevant articles.

Conclusions

The implementation of closed-loop systems in anesthesia practice represents an evolving field, showing promise in enhancing the precision and safety of drug administration across various applications, including hypnosis, hemodynamics, and relaxation. While significant heterogeneity among studies makes it challenging to definitively establish the superiority of closed-loop systems over manual administration, notable advantages have been reported, particularly in terms of prolonged time on target and reduced instances of undershooting and overshooting. However, the need for vigilant supervision and the ability to respond to unforeseen events or system malfunctions underscores the ongoing requirement for human expertise in anesthesia practice. Future research endeavors should strive to address the limitations of existing studies, including the exploration of muscle relaxation and the standardization of outcome measures, to further elucidate the potential benefits of closed-loop anesthesia systems.

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Data Availability Statement: All data and materials related to this scoping review are available upon request.

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