International Research Journal on Advanced Engineering and Management
https://goldncloudpublications.com
https://doi.org/10.47392/IRJAEM.2026.0163
e ISSN: 2584-2854
Volume: 04 Issue: 04
April 2026
Page No: 1062 - 1068

Hands-On to Hands-Free: The Evolution of Closed-Loop Drug Delivery System In Modern Anesthesia

Sheba Cherian[1], Nayara Afza Mufeed[2], Saniya J[3], Shivanagesham M[4], Soujanya S[5], Jaison Raju [6]
[1]Assistant Professor – Anesthesia and Operation Theatre Technology, Yenepoya School of Allied and Healthcare Professions, Yenepoya (Deemed to be University), Bangalore, Karnataka.
[2,3,4,5,6] PG – Anesthesia and Operation Theatre Technology, Yenepoya School of Allied and Healthcare Professions, Yenepoya (Deemed to be University), Bangalore, Karnataka.
Email: *shebacherian.blr@yenepoya.edu.in[1], 39155@yenepoya.edu.in[2], 39157@yenepoya.edu.in[3], 39195@yenepoya.edu.in[4], 46867@yenepoya.edu.in[5], 46737@yenepoya.edu.in[6]*

Abstract
Traditionally, the administration of anesthesia has been managed by Anesthesiologists with constant adjustments and tweaks based on a combination of clinical and physiological parameters. Although this system has been effective for decades, it has its own disadvantages—human errors and the problem of determining the appropriate depth of anesthesia, which may result in the administration of more than the required amount. Progress in monitoring tools, pharmacokinetic stimulations, and algorithmic controls has spurred the creation of a closed-loop anesthesia delivery system (CLADS), which automates drug delivery through continuous feedback. To outline the historical progression of CLADS across key periods in contemporary anesthesia practice and assess their clinical impact, we performed a scoping systematic review following PRISMA-ScR standards. Searches of electronic databases identified studies on the design, testing, and use of CLADS. Data were abstracted and analyzed; CLADS development was grouped into eras defined by monitoring techniques, control mechanisms, and degrees of automation in the clinical sector. The initial manual phase depended on anesthesiologist-directed dosing based on vital signs and expert assessment. Semi-automated advancement brought target-controlled infusions and the Bispectrality index to guide adjustments. Fully closed-loop systems combined live anesthesia depth tracking with dynamic algorithms for automatic dosing of drugs. The new hands-free phase leverages multi-source data, machine learning, and AI for tailored, adaptive delivery requiring little human input. CLADS's development from manual hands-on to completely hands-free automation represents a shift in the fundamentals to more exact, standardized, and personalized anesthesia practices. Understanding the highlights of each era underscores CLADS's promise to enhance safety, reduce variability, and redefine automated perioperative practices.

Keywords: *Closed-loop anesthesia delivery systems (CLADS), Automation, Target-controlled infusion (TCI), Bispectrality index (BIS), Machine learning/Artificial intelligence (AI)*

1. Introduction
The development of drug delivery systems represents a milestone in modern medicine and follows a pattern from crude beginnings to the highly advanced systems used today. In anesthesiology, such systems may be divided into distinct eras based on the level of technological input and control involved.

1.1. Era I: The Manual "Hands-On" Phase (Mid-20th Century – 1980s)
In the past, anesthesia delivery techniques were based on a "hands-on" method. Although attempts at automated anesthesia delivery date back to the 1950s with Bickford's early designs, serious attempts at automated anesthesia delivery began only in the 1980s. This "hands-on" period, spanning several decades, required the anesthesiologist to adjust fresh gas flow and infusion rates based on physiological signs. This method is also limited by the human ability to respond to physiological signs. This period also required the anesthesiologist to maintain the "triad of anesthesia" consisting of hypnosis, analgesia, and muscle relaxation solely based on his or her intuition and interpretation of physiological

International Research Journal on Advanced Engineering and Management
https://goldncloudpublications.com
https://doi.org/10.47392/IRJAEM.2026.0163
e ISSN: 2584-2854
Volume: 04 Issue: 04
April 2026
Page No: 1062 - 1068

signs such as pupil size and heart rate. Although "expert algorithms" were developed as part of computerized anesthesia delivery techniques in the past, they were also limited by the lack of means to assess drug effect in real time [1].

1.2. Era II: The Semi-Automated Phase (1990s)

The 1990s saw the advent of monitoring tools and computer-based models that combined the concept of hands-on control with the use of automation. In 1992, the Bispectrality Index (BIS) monitoring system was introduced. This provided an objective read of the depth of anesthesia. At the same time, Target Controlled Infusion (TCI) technology was also introduced. The term "TCI" first appeared in publications in 1992. The first commercial Diprifusor systems were also introduced in 1996. This allowed for more accurate targeting. Again, the human operator was the primary controller. This was an open-loop system. Compartmental pharmacokinetic (PK) and pharmacodynamic (PD) models provided the mathematical base for TCI systems. This allowed drugs to be given based on plasma concentration. This was also the time when Patient Controlled Analgesia (PCA) and Sedation (PCS) systems became popular. This provided the patient with a feedback role as they gave themselves medication within predetermined limits [2].

1.3. Era III: The Fully Closed-Loop Phase (Early 2000s – 2010s)

However, as we entered a new millennium, there appeared new systems capable of reading real-time physiological signals and adjusting drug dosage automatically, without human intervention. Clinical trials conducted in the early 2000s proved that CLADS could function effectively if BIS was chosen as a control variable. By 2010, commercial automated systems such as End-tidal Control of inhalational anesthetic became available in Europe, which kept anesthetic concentrations constant without human intervention and performed just as well as human control [3]. This era also saw the development of sophisticated control strategies such as Model Predictive Control and PID controllers, which can handle non-linear systems such as anesthesia control [4]. Pioneering systems such as "McSleepy" took control to a new level, attempting to control three aspects of anesthesia simultaneously: hypnosis, analgesia, and neuromuscular blockade. At the same time, there has been an investigation into adaptive control strategies such as L1 Adaptive control to deal with patient variability and to maintain stability in a wide range of patients.

1.4. Era IV: The Future "Hands-Free" and AI Phase (2010s – Present)

The modern period, spanning the 2010s till the present day, represents the trend towards "hands-free" systems with AI and telemedicine. Research and review articles published between 2015 and 2024 represent this period as the "era of human supervisory control," with AI controlling the drugs while the anesthesiologist monitors the patients remotely. This period also represents the development of AI-assisted drug formulation and prediction. This could change the role of the anesthesiologist from a technician to a system overseer. New "intelligent control systems" use neural networks such as RBF-NN-PID controllers with meta-heuristic algorithms for more precise titration of the infusion rates and the depth of anesthesia with fewer errors and more rapidly reaching a steady state. In addition to the development of AI-assisted drug formulation and prediction, the field has also witnessed the development of robotic systems for airway management, such as the Da Vinci and Kepler systems for intubation. Another development is the use of Anesthesia Information Management Systems (AIMS), which facilitates record-keeping and prediction of potential adverse events [5].

2. Method

This scoping review process was based on the Arksey and O'Malley model and followed the JBI guidelines for the PRISMA-ScR checklist. The process involved five major steps: developing a question for review, digging through the literature, selecting relevant studies that meet the criteria, charting data at the level of automation, and finally, weaving it all together. The process involved retrieving relevant articles from various sources that were deemed important for this review, and two researchers made a joint decision on which articles were relevant to this study. Data extraction involved technological milestones that

International Research Journal on Advanced Engineering and Management
https://goldncloudpublications.com
https://doi.org/10.47392/IRJAEM.2026.0163
e ISSN: 2584-2854
Volume: 04 Issue: 04
April 2026
Page No: 1062 - 1068

made automation possible, with automated systems integration in mind at all times. It was a process that highlighted this evolutionary path's impact on anesthesia practice from traditional titration to precision-guided systems and finally, bringing together what this new paradigm in challenges and opportunities in providing personalized anesthesia care with AI.

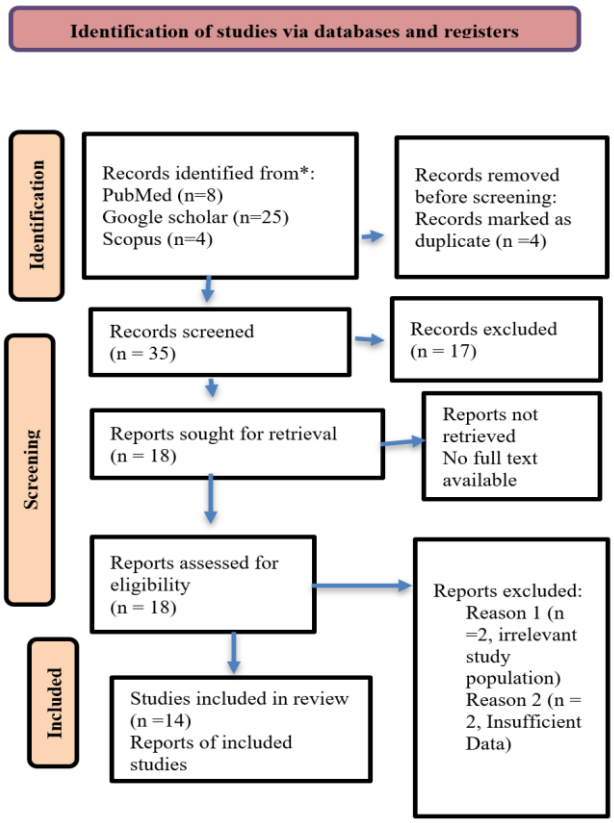

Figure 1 PRISMA- ScR Flow Chart - PRISMA Flow Diagram for the scoping review process

2.1. Data Charting

A standardized data extraction form was developed to capture key information relevant to the objectives of this scoping review and was prepared using Microsoft Word, as recommended for structured data charting in scoping review methodology (Arksey & O'Malley, 2005; Peters et al., 2020). Based on feedback and discussion among the review team, necessary modifications were made before applying the form to all included studies. The data charting process was guided by methodological recommendations for scoping reviews provided by the Joanna Briggs Institute (Peters et al., 2020).The following information was extracted from each study that included: author(s), year of publication, country of study, study design, characteristics of the study population, sample size, closed-loop system, drug-controlled, monitoring parameter, control algorithm, primary outcome, study gaps, key finding, study limitation, and comparator [6]. This information enabled the mapping of existing evidence on technological evolution and clinical impact of the closed-loop drug delivery system in modern anesthesia.

3. Results and Discussion

3.1. Results

The process of selection, as per the study, is presented through a PRISMA flow diagram. To obtain literature, databases such as PubMed, Scopus, and Web of Science were searched. Initially, 37 articles were retrieved. After eliminating duplicates, 35 articles were left, which were further screened according to the inclusion criteria, resulting in 17 articles being excluded. Further, a deeper assessment of the articles was done by reading the title, abstract, and content of all the articles, which resulted in 4 more articles being excluded. Finally, 14 articles were left, which were included according to the inclusion criteria [7].

3.2. Discussion

In this scoping review, anesthesia drug delivery is examined in relation to the evolution from manual adjustments to fully automated and closed-loop delivery. From an analysis of 14 studies, the evidence points to the fact that Closed-Loop Anesthesia Delivery Systems (CLADS) indeed mark a significant change in that they are precise, safe, and efficient compared to traditional methods.

- Technological Evolution

This is best exemplified by the history of CLADS, where there is a clear progression towards more objective, rather than subjective, dosing. Initially, there were manual dose adjustments, which were gradually replaced by semi-automated techniques such as Target Controlled Infusion (TCI) that utilized pharmacokinetic and pharmacodynamic models to achieve desired plasma concentrations. Significantly, the introduction of the Bispectral Index (BIS) [8]

International Research Journal on Advanced Engineering and Management
https://goldncloudpublications.com
https://doi.org/10.47392/IRJAEM.2026.0163
e ISSN: 2584-2854
Volume: 04 Issue: 04
April 2026
Page No: 1062 - 1068

Table 1 From Manual to Closed-Loop: Comparative Insights in Anesthesia

Sl. No	Author / Year / Country	Objective	Study Design	Sample Size	Drug Controlled	Monitoring Parameters	Control Algorithm	Primary Outcome	Study Gaps	Limitations	Comparator
1	Melissa D. McCabe et al., 2024, USA	Evaluate automated end-tidal control vs manual	RCT (non-inferiority)	209	Sevoflurane	EtAA, EtO_2, vitals	End-tidal control (EtC)	Non-inferiority in maintaining EtAA & EtO_2	US-only, elective non-cardiac cases	Not blinded, protocol deviations	Manual titration
2	Melissa D. McCabe et al., 2024, USA	Same as above	RCT (non-inferiority)	209	Sevoflurane	EtAA, EtO_2, vitals	End-tidal control (EtC)	Same outcome	Same gaps	Same limitations	Manual titration
3	Tsuyoshi Ikeda et al., 2025, Japan	Compare infusion vs bolus remimazolam	Prospective RCT	67	Remimazolam	MOAA/S, EEG entropy, vitals	Not automated	Faster LOC with bolus, less drug use	Single centre	Small sample, low-risk patients only	Infusion vs bolus
4	Meghna Singhal et al., 2023, multi-country	Review early closed-loop systems	Pilot & observational	<100	Propofol, Remifentanil, Sevoflurane	BIS, EEG, hemodynamics	PID, MPC, adaptive control	Improved depth control & safety	Limited RCTs	Data bias, lack of real-world trials	Manual, TCI, open-loop
5	Heena Chhanwal et al., 2022, India	Compare BIS vs standard dosing	Prospective RCT	100	Propofol	BIS, vitals, $ETCO_2$	BIS-guided titration	Reduced awareness, lower drug use	Single centre	Self-reported outcomes	Fixed-dose regimen
6	M. Ralph et al., 2011,	Evaluate adaptive	Simulation study	7	Isoflurane	BIS, hemodynamics	L1 adaptive contro	High BIS tracking	No clinical testing	Based on healthy volunte	PK-PD, neural network

International Research Journal on Advanced Engineering and Management
https://goldncloudpublications.com
https://doi.org/10.47392/IRJAEM.2026.0163
e ISSN: 2584-2854
Volume: 04 Issue: 04
April 2026
Page No: 1062 - 1068

	USA	controller					ller	accuracy		ers	s
7	Ammar T. Namel et al., 2023, Iraq	Evaluate automated systems	RCT & feasibility	7–83	Propofol, Remifentanil	BIS, EEG, vitals	PID, MPC, adaptive	Better stability, reduced drug use	Limited large trials	Patient variability issues	Manual, TCI
8	Shiwani Surjuse et al., 2023, multi-country	Review automation technologies	Pilot, RCT, simulation	<100	Multiple agents	BIS, EEG, TOF, CVI	PID, MPC, AI, RL	Improved stability, recovery	Few large RCTs	Ethical, technical issues	Manual, TCI
9	Elsayed Abdelzaam et al., 2020, Egypt	Review closed-loop systems	Mixed studies	<100	Propofol, inhalational	BIS, EEG, vitals	PID, MPC, adaptive	Better control, less drug use	Limited RCTs	EEG lag, variability	Manual systems
10	Prasanna Bidkar et al., 2023, India	Evaluate control systems	Pilot & RCT	10–100	Propofol, opioids	BIS, EEG, vitals	PID, MPC, AI	Improved control	Limited high-risk data	Regulatory issues	Manual, TCI
11	Mohammed Alyahya et al., 2024, Saudi Arabia	Review sedation systems	RCTs, meta-analysis	NA	Propofol, Remifentanil	BIS, PSI, vitals	PID, MPC, adaptive	Better sedation stability	Need multicenter trials	Automation bias	Manual, TCI
12	G.D. Puri et al., 2007, India	Evaluate CLADS vs manual	Prospective RCT	40	Propofol	BIS	PID adaptive	Better BIS control, less drug use	Small sample	Not generalizable	Manual titration

International Research Journal on Advanced Engineering and Management
https://goldncloudpublications.com
https://doi.org/10.47392/IRJAEM.2026.0163
e ISSN: 2584-2854
Volume: 04 Issue: 04
April 2026
Page No: 1062 - 1068

13	Max Liberman et al., 2013, USA	Develop BSP-based control	Simulation + animal	Rodents	Propofol, Etomidate	BSP (EEG)	PI controller	Accurate suppression tracking	No human trials	Simulation only	Manual, BIS systems
14	Hassanian Taghi et al., 2025, Iraq	Review drug delivery systems	Narrative review	NA	Various	PK, bioavailability	AI, nanotech	Improved drug delivery	Regulatory barriers	Experimental stage	Conventional systems

these "open-loop" techniques to evolve into "closed-loop" devices that could adjust dosages in real-time (Chhanwal et al., 2022; Puri et al., 2007). More recent developments have allowed devices such as McSleepy to utilize sophisticated controllers such as Model Predictive Control and PID controllers to manage hypnotic, analgesic, and muscle relaxant effects shown in Table 1.

- Clinical Impact

Overall, CLADS outperformed the manual practice in all the settings. For example, the use of automated systems ensured the control of the depth of anaesthesia, minimized the use of drugs, and ensured faster recoveries. For instance, the use of BIS-based CLADS protocols resulted in the reduction of intraoperative awareness and hemodynamic responses (Abdelzaam et al., 2020; Chhanwal et al., 2022) [9]. The use of End-Tidal Control Systems ensured the precise control of the depth of inhaled anesthetic agents and minimized clinical variability and environmental impact (McCabe et al., 2024). The studies thus show the potential use of automated systems in resolving the problems associated with human limitations.

- Future Directions

The frontier is no longer limited to hands-free devices, but rather includes a variety of devices such as artificial intelligence, telemedicine, and robots [10]. Neural network controllers, as well as meta-heuristic optimization, have shown significant promise in enhancing precision and stability. There is increasing use of robotic devices in airway management, and anesthesia information management systems (AIMS) form part of this new cyber-physical world. Thus, the role of the anesthesiologist is no longer that of a hands-on individual, but rather that of a controller, facilitating personalized care through technological aids [11]. (Alyahya et al., 2024; Taghi et al., 2025). However, the road ahead is not without its own set of challenges.

Conclusion

In conclusion, the change from "hands-on" manual control to "hands-free" automated control represents a paradigm shift in modern anesthesia. The evidence synthesized in the current review confirms that closed-loop control provides greater accuracy, less drug use, and improved patient safety compared with traditional approaches [12]. However, as we move into a new era of automated control with the aid of AI, it is crucial that we also focus on the validation of automated control in a variety of clinical situations, where it can be seen that it is an aid, rather than a replacement, for the crucial role of the anesthesiologist.

Acknowledgements

The authors thank Yenepoya (Deemed to be University), Bangalore, Karnataka, and the Department of Anesthesia and Operation Theatre Technology for providing institutional support and resources. This study received no external financial support and was conducted.

References

[1]. Taghi, H. S., Al-hakeem, M. A., & Almajidi,

International Research Journal on Advanced Engineering and Management
https://goldncloudpublications.com
https://doi.org/10.47392/IRJAEM.2026.0163
e ISSN: 2584-2854
Volume: 04 Issue: 04
April 2026
Page No: 1062 - 1068

Y. Q. (2025). The Evolution of Drug Delivery Systems: Historical Advances and Future Directions. Journal of Pharmacology and Drug Development, 3(1), 13-32.

[2]. Puri, G. D., Kumar, B., & Aveek, J. (2007). Closed-loop anesthesia delivery system (CLADS) using bispectral index: a performance assessment study. Anesthesia and intensive care, 35(3), 357–362. https://doi.org/10.1177/0310057X070350036

[3]. McCabe, M. D., Dear, G. D. L., Klopman, M. A., Garg, K., & Seering, M. S. (2024). End-tidal control versus manual control of inhalational anesthesia delivery: a randomized controlled noninferiority trial. Anesthesia & Analgesia, 139(4), 812-820.

[4]. TOMA, A. (2023). A Comprehensive Review on Automated Control of Anesthesia: Recent Methods, Challenges and Future Trends. Wasit Journal for Pure sciences, 2(2), 291-315.Meghna Singhal, Lalit Gupta , Kshitiz Hirani.

[5]. Singhal, M., Gupta, L., & Hirani, K. (2023). A comprehensive analysis and review of artificial intelligence in anesthesia. Cureus, 15(9).

[6]. Chhanwal, H., Kheskani, D., Gandhi, P., Shah, M. B., Makwana, D., & Rathod, V. (2022). Bispectral index: the current tool for monitoring unintended awareness and depth of anesthesia. Ain-Shams Journal of Anesthesiology, 14(1).

[7]. Bidkar, P. U., Dey, A., Chatterjee, P., Ramadurai, R., & Joy, J. J. (2024). Target-controlled infusion–Past, present, and future. Journal of Anesthesiology Clinical Pharmacology, 40(3), 371-380.

[8]. Elsayed Abdulsalam, Ehab Saeed Abd Allazeem & Dina H. Elbarbary (2020)

[9]. The effect of bispectrality index guided anesthesia versus standard practice on recovery after sevoflurane anesthesia in children: a prospective randomized double-blind clinical trial, Egyptian Journal of Anesthesia, 36:1, 250-255, DOI: 10.1080/11101849.2020.1838750.

[10]. Ralph, M., Beck, C. L., & Bloom, M. (2011, June). $\mathscr{L}$ 1-adaptive methods for control of patient response to anesthesia. In Proceedings of the 2011 American Control Conference (pp. 1729-1735). IEEE.

[11]. Alyahya, M. K., Almukhlifi, W. M., Albalawi, A. M. S., Al Dosari, M. N., Al Talasat, M. A., Alqarni, A. M., ... & Alharbi, Y. J. (2024). Remote and Automated Anesthesia: Telemedicine, Closed-Loop Systems, and the Future of Procedural Sedation. Saudi Journal of Medicine and Public Health, 1(2), 1467-1472.

[12]. Al-Araji, A. S., Dagher, K. E., & Abdullah, M. N. (2024). Development of Intelligent Control Strategy for an Anesthesia System Based on Radial Basis Function Neural Network Like PID Controller. International Journal of Intelligent Engineering & Systems, 17(3).