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GUIDELINE

Recommendation for the practice of total intravenous anesthesia

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Abstract

This Recommendation was developed by the Japanese Society of Intravenous Anesthesia Recommendation Making Working Group (JSIVA-WG) to promote the safe and effective practice of total intravenous anesthesia (TIVA), tailored to the current situation in Japan. It presents a policy validated by the members of JSIVA-WG and a review committee for practical anesthesia management. Anesthesiologists should acquire and maintain the necessary knowledge and skills to be able to administer TIVA properly. A secure venous access is critically important for TIVA. To visualize and understand the pharmacokinetics of intravenous anesthetics, use of real-time pharmacokinetic simulations is strongly recommended. Syringe pumps are essential for the infusion of intravenous anesthetics, which should be prepared according to the rules of each individual anesthesia department, particularly with regard to dilution. Syringes should be clearly labeled with content and drug concentration. When managing TIVA, particularly with the use of muscle relaxants, monitoring processed electroencephalogram (EEG) is advisable. However, the depth of sedation/anesthesia must be assessed comprehensively using various parameters, rather than simply relying on a single EEG index. TIVA should be swiftly changed to an alternative method that includes inhalation anesthesia if necessary. Use of antagonists at emergence may be associated with re-sedation risk. Casual administration of antagonists and sending patients back to surgical wards without careful observation are not acceptable.

Keywords Total intravenous anesthesia · Recommendation · Japan

Abbreviations

TIVA	Total intravenous anesthesia
JSIVA	Japanese Society of Intravenous Anesthesia
JSIVA-WG	The Japanese Society of Intravenous Anesthesia Recommendation Making Working Group
JSA	Japanese Society of Anesthesiologists
PONV	Postoperative nausea and vomiting
PK	Pharmacokinetics
PD	Pharmacodynamics
TCI	Target-controlled infusion
CSHT	Context-sensitive half-time
CSDT	Context-sensitive decrement time
AAGA	Accidental awareness during general anesthesia
PRIS	Propofol infusion syndrome
pEEG	Processed electroencephalogram monitor
BIS	Bispectral index

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PSI	Patient state index
SQI	Signal quality index
SR	Suppression ratio
EMG	Electromyography
DSA	Density spectral array
PPOU	Persistent postoperative opioid use
NMBA	Neuromuscular blocking agents

Introduction

As of 2024, total intravenous anesthesia (TIVA) is a widely used method of administering anesthesia, and is taught and practiced in many institutions. Numerous publications, including textbooks on TIVA techniques have been published, and new knowledge continues to expand through clinical research and case reports. However, guidelines or specific information produced by academic groups regarding practice of TIVA are not yet available in Japan. Therefore, the Japanese Society of Intravenous Anesthesia (JSIVA) herein presents a Recommendation on TIVA practice, with an aim to provide information for appropriate clinical decision-making when administering TIVA.

Based on the diverse TIVA methods used across institutions and by individual anesthesiologists, as well as previously limited published clinical evidence, the Japanese Society of Intravenous Anesthesia Recommendation Making Working Group (JSIVA-WG) and its review committee have developed this Recommendation to outline appropriate policies for TIVA practice.

It is recommended to refer to the drug information provided in the package inserts and the guidelines established by the Japanese Society of Anesthesiologists (JSA) when performing anesthesia practices, including TIVA.

Recommendation

1. Anesthesiologists should receive continuing education on TIVA, and acquire necessary knowledge and skills for safe practice.

Explanation:

While TIVA is widely utilized, inadequate proficiency in equipment operation and lack of basic pharmacological knowledge may cause severe complications such as intraoperative awareness [1]. Accurate knowledge and skills are essential to administer TIVA safely. Previous TIVA guidelines [2, 3] also emphasize the importance of education.

TIVA can be taught via on-the-job training, systematic lectures at educational institutions, and practical courses offered by academic societies and research groups. For example, the JSIVA has been providing hands-on lectures at its annual meetings since 2017.

This Recommendation does not specify the exact number of cases or duration required to be proficient in TIVA.

We recommend that practitioners possess the knowledge and skills listed in Table 1.

2. Ensure there is reliable venous access. Ideally, an entire route from a bag of fluid, three-way taps, intravenous tubing, and a venous catheter should be visible throughout the procedure. Monitoring infusion pump pressure and observation of drops falling through a chamber may help detect problems with a venous route.

Explanation:

In TIVA, drugs must be administered intravenously and PK simulations assume this to predict drug concentrations. If drug administration is interrupted, for example due to loose connections, kinked i.v. tubing, extravasation, or blockage of a catheter, it can lead to serious complications, such as intraoperative awareness and patient movement. Therefore, the entire route should, preferably, be visible, particularly with regard to connections and catheter insertion sites.

Intravenous anesthetics are commonly administered with an intravenous fluid serving as a carrier fluid. Thus, the carrier solution is desirable to be administered at a constant rate. When the fluid bag becomes empty, the infusion rate of intravenous anesthetic is significantly reduced and anesthetics can accumulate in the i.v. tubing. Upon resuming the carrier fluid infusion, concentrated anesthetics may be administered too quickly. To prevent this, always ensure that fluid drops are falling through the drip chamber, especially when adjusting the infusion rate manually with a clamp. When the carrier fluid is administered using an infusion pump, an air bubble detector can alert the attending anesthesiologist when the fluid bag has become empty. Additionally, monitoring infusion pressure can swiftly identify any blockages or kinks in the i.v. tubing.

3. Utilize real-time pharmacokinetic simulations whenever possible. If this is not feasible, gain experience with pharmacokinetic simulators specific to the anesthetics being used.

The plasma concentrations of anesthetics given in standard doses and clinical effects can be predicted to some extent. However, in reality, drug dosage needs to be adjusted in response to each patient's physiological status, as well as changing surgical stimuli. Information regarding the relationships between typical doses, plasma concentrations, and clinical effects may not be directly applicable in situations that deviate from standard circumstances, such as those illustrated in figures within drug information or literature.

Real-time PK simulation systems show the time course of plasma as well as the effect-site concentrations of

Table 1 Recommended knowledge and skills for practitioners of total intravenous anesthesia

Main items	Subitems	Action goals, etc
Understanding the clinical scenarios that favor the use of TIVA	Comparing TIVA with inhalational anesthesia	Detailing complications specific to inhalational anesthetics Outlining scenarios where TIVA is preferable over inhalational anesthesia [4] Elucidating the efficacy of TIVA in mitigating postoperative nausea and vomiting (PONV) [5, 6]
Grasping the significance of pharmacokinetics (PK) and pharmacodynamics (PD) in the context of TIVA	PK simulations Plasma concentration and effect-site concentration	Conducting PK simulations to visualize plasma and effect-site concentrations during and after drug administration Explaining the difference betweenplasma and effect-site concentrations Explaining the concept of target-controlled infusion (TCI) Implementing TCI when the conditions allow
	Transitional opioid	Converting the effect-site concentrations of fentanyl and remifentanil to each other [7] Transitioning from TIVA to postoperative analgesia using intravenous opioids If morphine is utilized, early administration is advisable due to the time lag to achieve maximum effect [8] Additionally, it is important to monitor for respiratory depression [9]
	Impact of patient characteristics on PK and PD: variations due to age, gender, and obesity	Explaining the variability in the predictions of plasma and effect-site concentrations by different PK models for the same anesthetic Selecting the optimal model for PK simulations for each patient Explaining how target plasma and effect-site concentrations can vary across different clinical scenarios
	TCI pump with Diprifusor system	Explaining the prediction accuracy of the Diprifusor system [10] Explaining that inputting ideal body weight may result in underdosing [11]
	Context-sensitive half-time (CSHT) and context-sensitive decrement time (CSDT)	Explaining the differences between CSHT and CSDT Specifically, describing scenarios where CSHT is short, yet CSDT is prolonged
	Weight correction in obese patients	Explaining the rationale for reducing anesthetic dosage per kilogram of body weight in obese patients, including its PK considerations
	Changes in PK and PD in the same patient	Explaining the effects of decreased hepatic blood flow [12], changes in cardiac output [13], and hemodilution [14]
	Hypoalbuminemia [15]	Explaining the increased efficacy of propofol in the context of hypoalbuminemia

Table 1 (continued)

Main items	Subitems	Action goals, etc
	Pharmacodynamic interaction	Explaining the concept of isobolograms and their application in assessing drug interactions Explaining the concept of the response surface model Performing TIVA with awareness of pharmacodynamic interactions between propofol and opioids Explaining the risk of accidental awareness in TIVA with propofol and opioids Performing TIVA with remimazolam and opioids, and explaining the precautions
	Selected anesthetics that require a deep understanding of PK and PD	Propofol [16–19] Remifentanil [20–23] Remimazolam [24–28] Fentanyl [29–31] Ketamine [32] Dexmedetomidine [33, 34]
Accidental awareness during general anesthesia (AAGA)	Epidemiology	Explaining the risk factors for AAGA Explaining that AAGA can leadtopost-traumatic stress disorder Explaining the importance of early detection and response to AAGA [1]
Equipment used for TIVA		Explaining the siphoning phenomenon Explaining the phenomenon in which it takes time for the pump flow rate to stabilize or the flow rate to fluctuate
	Characteristics of TCI pumps (TERUFUSION Syringe Pump Type TE-371 or SS3 TCI, Terumo, Tokyo, Japan) available in Japan	Understanding that the bolus administered using the priming button is not included in the total dose calculation Understanding that the only patient factor affecting the on-board PK model is weight
Troubleshooting		Deciding to interrupt TIVA and convert to alternative anesthetic methods
	Propofol	Assembling propofol pre-filled kits Managing vascular pain associated with propofol infusion [35] Possessing knowledge of propofol infusion syndrome (PRIS) [36], urine discoloration [37], and bacterial contamination
	Remifentanil	Managing glottal closure (especially with supraglottic airway device use) [38, 39], the lead pipe phenomenon, and shivering Explaining the risks associated with extremely high dosing
	Remimazolam	Being aware of the risk of obstructing an intravenous line when diluted at a high concentration Explaining the risks associated with uniform antagonism
	Ketamine	Being aware of the risks of increasedsaliva and nightmares
	Dexmedetomidine	Being aware of the risks of elevated blood pressure and bradycardia

Table 1 (continued)

Main items	Subitems	Action goals, etc
Processed electroencephalogram monitor (pEEG)		Explaining the importance of monitoring raw brain waves [40] Explaining situations where pEEG presents abnormal values [41] Explaining parameters other than sedation indices including bispectral index (BIS) or patient state index (PSI), such as signal quality index (SQI), suppression ratio (SR), and electromyography (EMG) Interpreting density spectral array (DSA)
Knowledge update	Recent topics related to TIVA	Acute tolerance and hyperalgesia associated with opioid use [42] Chronic pain [42] Persistent postoperative opioid use (PPOU) [43, 44] Possible risk of postoperative neurocognitive impairment associated with oversedation [45] Multimodal anesthesia approach [46, 47] Opioid-sparing and opioid-free anesthesia [48] Effect of anesthesia choice on the prognosis of patients with malignant tumors [49, 50] Utility of TIVA in cardiac anesthesia [51] Expanded indications for intravenous anesthetics (e.g., remifentanil in the intensive care setting)

intravenous anesthetics based on medication history. The information of PK simulation may facilitate adjustment of dosage and/or timing of anesthetic administration. As of 2024, PK simulators integrated into an electronic anesthesia record are becoming more and more widely used, while numerous stand-alone applications are also available for smartphones and personal computers. It should be noted that the present Recommendation does not endorse any specific PK simulation software.

Even if real-time PK simulators are unavailable, gaining experience with such a PK simulator during TIVA anesthesia or training would be useful and well advised. Such experience is invaluable to gaining an understanding of how plasma and effect-site concentrations change with dose adjustments.

4. For continuous administration of intravenous anesthetics, infusion pumps are essential devices. These pumps should be regularly inspected by a clinical engineer, to make sure that they are in proper working order and batteries are fully charged.

Explanation:

Intravenous anesthetics are administered either as a single dose or a continuous infusion. For a continuous infusion, a syringe pump is necessary to ensure accurate flow rate. The present Recommendation does not endorse any specific pump model or brand. Adjusting flow manually, for example by clamp manipulation, is usually inaccurate and thus discouraged.

As syringe pumps are sophisticated medical devices, they are prone to unexpected failures. Regular maintenance and periodic inspections are essential. These tasks should be conducted by qualified personnel, typically in a clinical engineering department, to ensure the reliability of the equipment. The batteries of the syringe pumps should be fully charged to maintain pump operation in case of AC power outage, and to prevent interruptions of drug delivery.

5. Each facility or department should make its own guidelines for dilution of intravenous anesthetics and clear labeling of syringes, to aid in easy identification. Drugs should be prepared according to dilution instructions provided in the package insert.

Explanation:

In Japan, anesthesia has been provided by a wide variety of physicians with variable experience. To prevent accidental overdose or underdose, all anesthesiologists should prepare drugs based on a common local rule in each department. Anesthetic dosage errors represent a significant risk in the operating room, as highlighted by numerous studies [52]. As many anesthetics have a narrow therapeutic index [53], which is the ratio between toxic dose and therapeutic dose, dilution errors can lead to either inadequate or excessive levels of anesthesia. Therefore, dilution of drugs should be standardized for patient safety. For easy identification of syringe contents, it is ideal to label both the syringes and the pumps clearly, using standardized labels with consistent placement. Safety protocols in each department should be regularly reviewed and renewed if necessary.

"Preventing medication errors in the perioperative setting: recommendations on drug syringe labels," [54] by JSA also advocates the standardization of drug syringe labels. There is a concern that relying on color alone may actually discourage reading of labels, leading to potential misinterpretations of syringe contents [55].

6. When TIVA is maintained with propofol, use TCI if feasible.

Explanation:

Propofol can be administered either by manually adjusted or TCI. In the former, anesthesia is induced with a propofol bolus of 1–2.5 mg/kg, followed by maintenance infusion at a rate of 4–10 mg/kg/h, as detailed in the Guidelines for the Use of Anesthetics and Related Drugs, 3rd edition. [56] In TCI, a special syringe pump automatically adjusts the rate of infusion to attain and maintain the set target concentration. When both are feasible, TCI is favored as it is more user-friendly and contributes to safety.

Note: TCI systems that directly control effect-site concentrations are not currently available in Japan.

7. When managing TIVA, particularly with the use of muscle relaxants, the use of a processed EEG monitor is advisable. Comprehensive assessment should not only include the sedation level index, but also consider the accuracy of input signals, contamination of myoelectric activity, presence of flat EEG, and evaluation of EEG waveforms. It is crucial to ensure the maintenance of an optimal sedation level, taking into account individual patient characteristics and the varying degrees of surgical invasiveness.

Explanation:

In July 2014, JSA included conditional use of EEG monitors in the third revision of "Monitoring Guidelines for Safe Anesthesia" [57]. Assessment of sedation level using processed EEG monitors is a key component of contemporary anesthesia management. These monitors provide an index by analyzing EEG obtained from the patient's forehead. Intraoperative EEG waves may be interfered by various factors [41]. Notably, the index of processed EEG is influenced by facial EMG, potentially leading to misjudgment of anesthesia level [58, 59]. NMBA

can artificially lower the processed EEG index; in addition, high-dose opioids lower EEG frequency [60]. Moreover, EEG signal complexity increases when sedatives with different mechanisms of action are co-administered [61, 62]. Cerebral blood flow, hypovolemia, hypoxemia, and hypothermia can also affect EEG monitoring.

8. TIVA should be changed to an alternative method including inhalation anesthesia, if necessary.

Explanation:

TIVA can be applied in most anesthesia cases, including those which require intraoperative neurophysiological monitoring such as motor evoked potentials. However, variability in patient's PK/PD or difficulties in accurate assessment of level of anesthesia may sometimes make it impractical to maintain with TIVA. Under those circumstances, anesthesiologists should consider an alternative method that includes inhalation anesthesia. For example, in patients with remimazolam tolerance, consider changing the primary anesthetic responsible for sedation to propofol or inhalation anesthetics [63–65].

This also applies when adverse reactions to intravenous anesthetics occur or equipment fails.

9. Use of antagonists is associated with risks of re-sedation and other side effects. Uniform reversal of anesthesia with antagonists is not recommended.

Explanation:

The effects of benzodiazepines (such as midazolam and remimazolam) can be antagonized by flumazenil. However, after the effect of flumazenil has worn off, re-sedation may occur [66], and re-respiratory depression might also occur. Moreover, in chronic users of benzodiazepines for epilepsy or other neurological disorders, convulsions may occur when flumazenil rapidly antagonizes the effects of benzodiazepines.

Naloxone may be administered to reverse residual ventilatory depression due to opioids (morphine, fentanyl, and remifentanil). Acute reversal of opioid effects may lead to exacerbation of postoperative pain.

Therefore, antagonists should be administered carefully with awareness of their adverse effects and possibility of re-sedation. Administration of high dose of antagonists is not recommended. Antagonists should be given in small, divided dose, according to the manufacturer's instructions.

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