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Original Article

Total intravenous anesthesia for major burn surgery

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Abstract: Total intravenous anesthesia (TIVA) is frequently used for major operations requiring general anesthesia in critically ill burn patients. We reviewed our experience with this approach. Methods: During a 22-month period, 547 major burn surgeries were performed in this center's operating room and were staffed by full-time burn anesthesiologists. The records of all 123 TIVA cases were reviewed; 112 records were complete and were included. For comparison, 75 cases were selected at random from a total of 414 non-TIVA general anesthetics. Some patients had more than one operation during the study: as appropriate for the analysis in question, each operation or each patient was entered as an individual case. For inter-patient analysis, exposure to 1 or more TIVAs was used to categorize a patient as member of the TIVA group. Results: Excision and grafting comprised 78.2% of the operations. 14 TIVA regimens were used, employing combinations of 4 i.v. drugs: ketamine (K, 91 cases); i.v. methadone (M, 62); fentanyl (F, 58); and propofol (P, 21). The most common regimens were KM (34 cases); KF (26); KMF (16); and K alone (8). Doses used often exceeded those used in non-burn patients. TIVA was preferred for those patients who were more critically ill prior to surgery, with a higher ASA score (3.87 vs. 3.11). Consistent with this, inhalation injury (26.7 vs. 1.6%), burn size (TBSA, 36.3 vs. 15.8%), and full-thickness burn size (FULL, 19.8 vs. 6.5%) were higher in TIVA than in non-TIVA patients. Despite this, intraoperative pressor use was as common in TIVA as in non-TIVA cases (23.9 vs. 22.7%). Conclusions: TIVA was used in patients whose inhalation injury rate and TBSA were greater than those of non-TIVA patients. TIVA cases were not associated with increased hemodynamic instability. TIVA is a viable approach to general anesthesia in critically ill burn patients.

Keywords: Total intravenous anesthesia (TIVA), burn, surgery

Introduction

For many years, intravenous ketamine has been used for brief, painful ward procedures in burn patients, such as dressing changes and debridement of eschar during hydrotherapy. Ketamine has also formed the basis for total intravenous anesthesia (TIVA) provided for excision and grafting of the burn wound. Proponents of this approach point to the favorable hemodynamic characteristics of ketamine, the maintenance of spontaneous respiration, and the excellent anesthesia, analgesia, and amnesia achievable. On the other hand, use of ketamine without a concomitant benzodiazepine has been associated with emergence phenomena in adults. Inhalational general anesthesia may be more convenient for procedures performed in the operating room, and many anesthesia providers are more experienced with this approach.

At the U.S. Army Burn Center (U.S. Army Institute of Surgical Research), high-frequency percussive ventilation employing the Volumetric Diffusive Respiration (VDR-4®) ventilator (Percussionaire, Sandpoint, ID) has been used preferentially for the intensive care unit (ICU) care of intubated patients with smoke inhalation injury for several years [1]. Furthermore, this mode of ventilation may be continued in the operating room, because of experience suggesting that patients with significant lung injury may develop atelectasis and decreased oxygenation if transferred from the VDR-4® to a standard anesthesia ventilator. This mandated the use of TIVA for the intraoperative anesthetic management of these patients, since the VDR-4® is not approved for the delivery of anesthetic gases. Thus, anesthesiologists at this center have gained significant experience with TIVA in critically ill burn patients undergoing major burn surgery. The purpose of this study was to review

Table 1. Patient Data

	TIVA	Inhal. Anes.	*p* value
Number	45	62	
Age (y)	35.6±18.0	35.2±18.3	(.929)
TBSA (%)	36.3±20.0	15.4±14.0	.0000
FULL (%)	19.8±19.5	6.0±11.4	.0001
Smoke Inj.	12 (26.7%)	1 (1.6%)	.0001
Death	8 (17.8%)	3 (4.8%)	.0496*

*Two-sided Fisher's exact test. TBSA, total body surface area burned, percent. FULL, full thickness burn size, percent. Smoke Inj., presence of smoke inhalation injury. TIVA, patient received at least one total intravenous anesthesic. Inhal. Anes., patient received an inhalational anesthetic during the hospital stay, and did not receive TIVA (see text).

Table 2. Type of Operation

	TIVA	Inhal. Anes.
Excision & grafting	78 (69.6%)	69 (92%)
All other operations (enumerated below)	34	6
Debridement	10	2
Tracheostomy	9	0
Abdominal	7	0
Amputation	5	0
Plastics/other	1	3
Fasciotomy	2	1

this experience and, in particular, to characterize the various regimens employed (to include, but not limited to, those based on ketamine).

Materials and methods

A retrospective chart and database review was conducted for a 22-month period. All TIVA cases performed during this period of time were identified and included in this study (n=112). A random sample of the 425 inhalational anesthesia cases performed during the same period was also identified and included for comparison (n=75). Operative excision and grafting of deep partial and full-thickness burn wounds was typically performed within one week of injury. The operating room was not used for initial cleansing of the burn wound or for subsequent non-surgical dressing changes; these procedures were performed in the ICU or ward and were not included in this study. Some patients received TIVA early during the ICU phase of their hospital stay, and inhalational anesthesia later.

For analyses in which each patient was entered as an individual case (to include analysis of mortality), patients were classified as TIVA patients if they received one or more TIVA operations, and as non-TIVA patients if they did not. Data were analyzed with SPSS v. 10.1 software (SPSS, Chicago, IL). Univariate analysis employed the chi square test, Fisher's exact test, or independent samples t test, as appropriate. Stepwise logistic regression analysis (backward-likelihood-ratio method) was used to evaluate variables as candidate predictors of mortality. Variables analyzed in this fashion included total burn size (TBSA), full-thickness burn size, age (represented as an age function) [2], the presence of inhalation injury, and whether or not the patient received TIVA. Data are presented as means±SD unless otherwise noted. Significance was accepted at $p<0.05$. This study was approved by the Institutional Review Board (IRB).

Results

Forty-five patients underwent 112 TIVA operations during the study period. In the comparison group, 62 patients underwent 75 operations under inhalational anesthesia. Patient data are presented in **Table 1**. As expected, TIVA patients had a higher total burn size (TBSA), full-thickness burn size (FULL), incidence of inhalation injury, and mortality.

The type of operation performed is given in **Table 2**. Excision and grafting of the burn wound was the most frequent operation performed in both TIVA and inhalational cases. Other types of surgeries were more frequently performed under TIVA than under inhalational anesthesia (p=.0003). These surgeries were those associated with critical illness in burn patients, to include debridement of wounds without grafting, tracheostomy, laparotomy, and amputation. **Table 3** indicates the increased acuity of surgeries performed under TIVA. TIVA patients had higher American Society of Anesthesiologists Physical Status classification (ASA) scores, had longer operative times, and received more blood. However, there was

Table 3. Acuity of Operation

	ASA score	RBC units	Plasma units	Platelet 6-packs	Pressors	Op time
TIVA	3.87±0.49	2.0±2.9	0.3±1.0	0.1±0.6	17 (22.7%)	2.9
Inhal. Anes.	3.11±0.92	1.0±1.5	0.0±0.0	0.0±0.0	27 (23.9%)	2.5
p value	.0000*	.002	.004	.043	.846	.017

ASA score, American Society of Anesthesiologists Physical Status classification. RBC units, number of units of packed red blood cells transfused during the operation. Plasma units, number of fresh-frozen plasma units transfused. Platelet 6-packs, number of six-unit packs of platelets transfused. Pressors, use of alpha-adrenergic agents by injection or continuous infusion during the operation. Op time, operating time in hours. *Chi square analysis of the 2x5 table.

Table 4. Anesthetic Regimens Used for TIVA

Regimen	n
KM	34
KF	26
KMF	16
K	8
KFP	7
F	5
KMP	3
MP	3
MFP	3
KP	3
MF	2
FP	1
KMFP	1

K, ketamine; m, methadone (i.v.); f, fentanyl; p, propofol.

no difference in pressor requirements. It was not our practice during the timeframe of this study to record the surface area grafted during these operations.

In **Table 4**, it can be seen that ketamine was the basis for the majority of TIVA anesthetics used. Ketamine was most frequently combined with an intravenous (i.v.) narcotic, such as methadone, fentanyl, or both. Propofol was used less frequently. **Table 5** gives dose ranges for the most commonly used drug regimens. To calculate these doses, it was necessary to sum both initial and subsequent bolus injection doses, and continuous infusion doses, since the drugs were often given in all 3 fashions. In addition, patients receiving ketamine TIVA were routinely premedicated with midazolam. In these heavily sedated ICU patients, emergence phenomena following ketamine use were not noted.

In **Table 6**, the impact of various factors on mortality is presented. Again, for this analysis, TIVA patients are those who received at least one TIVA. By univariate analysis, as shown in the table, age, TBSA, FULL, and TIVA, but not inhalation injury, were all associated with increased mortality. By logistic regression, however, only TBSA and age (the latter as a cubic age function) were retained in the following equation for the probability of death:

P (mortality) = e^k / (1-e^k), where k = .048*TBSA + 2.035*AgeFn - 3.636, and AgeFn = (- 5*age + 14*age^2/100 - 7*age^3/10000) / 100.

Thus, increased mortality in the TIVA patients was explained by their larger burn size.

Discussion

The principal findings of this study were: (1) TIVA, based principally on ketamine, was safely and effectively used in critically ill burn patients. (2) Despite more extensive burns and operations of greater complexity requiring transfusion of more blood, the pressor requirements during TIVA cases were not greater than for those for inhalational anesthesia cases. (3) Most commonly, ketamine was combined with a narcotic to include i.v. methadone. Doses used for TIVA varied widely. (4) Emergence phenomena were not identified, most likely due to the concomitant use of midazolam or (less frequently) propofol.

Since the majority of the cases reported here employed ketamine-based TIVA, a discussion of this drug's role in the burn center is warranted. Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and interacts with several other receptors as well. It is a racemic mixture of 2 optical enantiomers, S(+) ketamine and R(-) ketamine. It is classically described as a dissociate anesthetic, producing, as well, amnesia, analgesia, and immobility [3, 4].

Several features make ketamine attractive for use in patients with burns, sepsis, or hemor-

Table 5. Regimen Doses

Regimen	n	Ketamine mg/kg/h	Methadone mg/kg	Fentanyl mcg/kg/h
KMF	16	8.6 (0.2-28)	0.54 (0.1-0.81)	8.6 (0.2-23)
KM	34	8.3 (0.15-15.5)	0.26 (0.26-1.6)	0
KF	26	5.4 (0.5-1.7)	0	10.3 (1.3-40)
K	8	4.5 (1.8-11)	0	0

Doses given are medians with ranges.

Table 6. Mortality

	Live	Die	*p* value
Age	34.1±17.0	46.5±23.8	.031
TBSA	22.7±18.6	37.1±24.8	.020
FULL	10.6±14.6	22.7±28.3	(.189)
Smoke Inj.	10 (10.0%)	3 (27.3%)	(1.0)*
TIVA	37 (38.5%)	8 (73.7%)	.0496*

*Two-sided Fisher's exact test.

rhagic shock. It has frequently been used in burn centers, particularly for frequent debridements, dressing changes, and tanking (hydrotherapy) procedures outside of the operating room [5-7]. The advantages of the drug in this setting include its analgesic efficacy, maintenance of airway reflexes, and sympathomimetic effects producing hemodynamic stability [8]. In many U.S. hospitals, ketamine (regardless of dose) is now classified as a drug for which conscious sedation procedures are required. This potentially limits its utility, and Owens et al. recently described a program whereby its administration on the burn ward by a non-anesthesiologist team is performed [9].

Ketamine has anti-inflammatory effects on neutrophil activation and on cytokine production which may be important in burn patients. Ketamine reduced the migration of neutrophils through human endothelial cell monolayers [10]. It reduced the expression of CD18 on, and the shedding of CD62L from, endotoxin-stimulated neutrophils [11]. Ketamine is not a reactive-oxygen-species scavenger [12], but reduced neutrophil production of superoxide (O_2-) after cardiopulmonary bypass [13]. Several studies document this drug's reduction of pro-inflammatory cytokine release following lipopolysaccharide (LPS) stimulation [14], staphylococcal enterotoxin B stimulation [15], and cardiopulmonary bypass [16]. At high doses, ketamine reduced myeloperoxidase and pro-inflammatory cytokine levels in the lung, ameliorating acute lung injury after endotoxin [17]. The mechanism for these effects on cytokine production is not fully understood. However, ketamine has been shown to reduce nuclear factor kappa-B production in the lung, brain, liver, and intestine [17-20]. Taken together, these findings suggest that ketamine may exert beneficial anti-inflammatory effects in patients with burns and or sepsis.

Ketamine is well-known to exert sympathomimetic effects, such that many patients respond with an increase in blood pressure, heart rate, and cardiac output [21]. The exact mechanism is still under investigation. In the periphery, the drug inhibits both neuronal and extraneuronal catecholamine uptake [22]. Because small doses of ketamine given into the cerebral circulation increased blood pressure and heart rate, it was concluded that it also increases central sympathetic outflow. However, racemic ketamine appears to exert a depressive effect on brainstem vasomotor centers [23]. Also, racemic ketamine decreases directly measured muscle sympathetic nerve activity (MSNA, a measure of sympathetic outflow), whereas S(+) ketamine increases MSNA and indeed further increases it in response to nitroprusside-induced hypotension [24, 25]. Finally, some of ketamine's effects on the blood pressure are actually mediated by inhibition of endothelial nitric oxide synthase (eNOS) [26]. Irrespective of the mechanism, ketamine's cardiovascular effects argue in favor of its use in hypovolemic patients. Also, by causing peripheral vasoconstriction, ketamine is advantageous in patients at risk for hypothermia [27]. Whether peripheral vasoconstriction occurs in patients with major burns, and whether this causes a reduction in blood loss, is unknown.

In denervated hearts or isolated myocardial preparations, however, ketamine has been shown to have a direct negative inotropic effect [28]. This effect can be counteracted by beta-adrenergic stimulation (isoproterenol) in myocardium from normal but not from failing hearts [29]. S(+) ketamine at low doses was found to have a positive inotropic effect, which R(-) ketamine lacked; at high doses, both isomers had negative inotropic effects, accompanied by a decrease in intracellular calcium gradients [28]. These negative inotropic effects probably explain why some critically ill patients may become hypotensive upon induction with ketamine. These "catecholamine-depleted" patients are, in fact, maximally stressed, and unable to release additional catecholamines in response to a decrease in cardiac output. For this reason, a lower initial i.v. dose of 0.25-0.5 mg/kg may be safer than the usual induction dose of 1.0-2.0 mg/kg for patients with, e.g., burn shock or septic shock.

Several conditions are typically considered contraindications to ketamine use, but many of these dogmas are being revised. As a dissociative anesthetic and in contrast to drugs such as propofol, ketamine may increase cerebral metabolic rate and intracranial pressure (ICP), and thus cause worsening of cerebral ischemia in brain-injured patients [30]. On the other hand, recent work indicates that ketamine's hemodynamic effects may increase cerebral perfusion pressure, that it does not increase ICP (under conditions of controlled ventilation, concomitant use of a GABA-receptor agonist, and avoidance of nitrous oxide) and that it may have neuroprotective effects [31]. Likewise, the concept that this drug causes increased intraocular pressure appears to be inaccurate [32].

Other disadvantages of ketamine include psychotomimetic emergence reactions, which occur in 5-30 percent of patients. These feature alterations in mood or body image, extracorporeal or dissociative experiences, floating sensations, vivid dreams or illusions, and/or delirium. However, the concomitant use of a benzodiazepine or propofol effectively prevents these phenomena, and they have not been a problem in our experience [4, 33]. Also, the S(+) enantiomer has a clinical potency with respect to the R(-) enantiomer of 2:1, allowing for faster recovery times and, possibly, a reduction in emergence phenomena. The S(+) enantiomer is approved for use in Europe [3].

More importantly, the use of ketamine for TIVA is complicated by a somewhat unpredictable dose-response relationship, requiring titration of the infusion rate. The advent of target-controlled infusion (TCI), in which the infusion rate for the drug is controlled by a computer based on a pharmacokinetic model, may improve the ease of use of this and other i.v. anesthetics [34]. It should be borne in mind that tolerance, requiring an increase in the induction dose, is common in burn patients who receive more than 2 exposures [8].

The logistical burden associated with inhalational anesthetics has made TIVA, and in particular ketamine-based TIVA, a mainstay of battlefield and third-world anesthesia. This was the case in Vietnam [35], the Yom Kippur War of 1973 [36, 37], the Falklands-Malvinas campaign [38, 39], civil war in Somalia [40], and the recent conflict in Iraq [41].

In conclusion, total intravenous anesthesia, based primarily on ketamine, was successfully used for major burn surgery performed on critically ill patients in this retrospective study. This approach was well tolerated from a hemodynamic standpoint, and psychotomimetic effects were effectively prevented by concomitant use of midazolam or propofol. We anticipate that the development of target-controlled infusion and S(+) ketamine will lead to wider acceptance of this approach to anesthetic management, both within the burn center and elsewhere.

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