Original Article

Comparison of effects of ketamine, ketamine-dexmedetomidine and ketamine-midazolam on dressing changes of burn patients

Murat Gündüz, Şefika Sakallı, Yasemin Güneş, Erol Kesiktaş, Dilek Özcengiz, Geylan Işık

Department of Anesthesiology, Çukurova University Faculty of Medicine, Çukurova State Hospital, Department of Plastic and Reconstructive Surgery, Adana, Turkey

Abstract

Objective: The aim of this randomized, controlled study was to compare the sedoanalgesic effects of ketamine-dexmedetomidine and ketamine-midazolam on dressing changes of burn patients.

Materials and Methods: Following Ethics Committee approval and informed patient consent, 90 ASA physical statuses I and II adult burn patients were included in the study. Patients were randomly divided into three groups. Ten minutes before dressing change, the dexmedetomidine group (group KD) (n = 30) received a continuous infusion of dexmedetomidine at a rate of 1 μg kg^{-1}, the midazolam group (group KM) (n = 30) received a continuous infusion of midazolam at a rate of 0.05 mg kg^{-1} and the saline group (group KS) (n = 30) received a continuous infusion of saline intravenously. One minute before dressing change, each patient was administered 1 mg kg^{-1} ketamine intravenously. Hemodynamic variables, pain and sedation scores, the number of patients requiring additional ketamine, time to dressing change and recovery time were recorded.

Results: Systolic blood pressure (SBP) values were significantly lower at, before and after ketamine administration; and 5, 10 and 15 minutes after the procedure in group KD in comparison with the other groups (P <0.05). There was no significant difference in pain scores among the groups during the study period. Sedation scores were significantly higher in group KD than in groups KM and KS at the end of the first hour (P <0.05). Time to dressing change and recovery time were similar in all the groups.

Conclusion: In burn patients undergoing dressing changes, although both combinations ketamine-dexmedetomidine and ketamine-midazolam offered an effective sedoanalgesia without causing any significant side effect, the former resulted in higher sedation and lower hemodynamic discrepancy.

Key words: Burn, dexmedetomidine, dressing changes, ketamine, midazolam

Introduction

Patients treated for burn injuries commonly experience high levels of acute pain and anxiety during hospitalization, particularly as it relates to their dressing changes and other medical procedures.[1-4]

Address for correspondence: Dr. Murat Gündüz,
Çukurova University Faculty of Medicine,
Department of Anesthesiology, 01330-Adana, Turkey.
E-mail: hmurat@cu.edu.tr

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Ketamine has been widely used in burn dressing changes during excision and grafting and for sedation. Ketamine remains a relatively safe drug; however, monitoring of these patients is essential, particularly since there are reports of respiratory and cardiovascular depression.[5-9]

Benzodiazepines are commonly used in burns units.[3,9,10] It is widely understood that pain is exacerbated by anxiety. In burns, the commonly used benzodiazepine is midazolam. Patients may receive midazolam by intravenous, intranasal, rectal or oral route. Ketamine is associated with emergence phenomena. Midazolam seems to somewhat help alleviate discomfort arising from these physchological reactions.[11]

Dexmedetomidine, a selective a2-adrenergic agonist, is being studied for its potential use in anesthetic practice because of its combined analgesic, sedative, hypnotic and anxiolytic effect.[12,13] Dexmedetomidine reduces the dose requirements of opioids and anesthetic agents and attenuates

the hemodynamic responses to tracheal intubation and surgical stimuli.[14] Horvath *et al.*[15] showed that endomorphin-1, like morphine, shows synergistic interaction with both the N methyl D aspartate(NMDA) antagonist S-ketamine and the a2-adrenoceptor agonist dexmedetomidine. The synergistic interaction between these drugs may be of therapeutic significance in the future, by allowing a decrease in the dose of either drug required to achieve an acceptable level of analgesia.

This study was designed to indicate the alternative methods of pain control and to compare the effects of ketamine, ketamine-midazolam and ketamine-dexmedetomidine on the hemodynamic variables, analgesia and sedation in burn patients undergoing dressing changes.

Materials and Methods

After receipt of Institutional Review Board approval and patients' written informed consent, 90 ASA I-III burn patients, between the ages of 19 and 65 years, scheduled for dressing changes with sedoanalgesia, were recruited. The study period was March 2006 to August 2007 (18 months). Patients were included in the study if total burn surface area (TBSA) was between 10% and 25%. Patients who were less than 18 years of age, pregnant or nursing; or had abnormal laboratory test results, hypersensitivity to opioids, significant psychiatric, cardiovascular, renal or hepatic diseases were excluded.

On arrival in the operating room of patients, routine monitors were applied for recording heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MBP), peripheral oxygen saturation (SpO_2), and urine output (bladder catheter). After obtaining baseline values and those 10 minutes before dressing change, patients were randomly (computer-generated random table) allocated to receive one of three study protocols.

Patients in group ketamine-dexmedetomidine (KD) (n = 30) received intravenous (IV) dexmedetomidine (1 μg kg^{-1}) over 10 minutes, before intervention, followed by 1 mg kg^{-1} of IV ketamine.

Patients in group ketamine-midazolam (KM) (n = 30) received IV midazolam (0.05 mg kg^{-1}) over 10 minutes, before intervention, followed by 1 mg kg^{-1} of IV ketamine.

Patients in group ketamine-saline (KS) (n = 30) received IV saline over 10 minutes, before intervention, followed by 1 mg kg^{-1} of IV ketamine.

The number of patients requiring additional ketamine; and the pain and sedation scores, time to dressing change and recovery time for all patients were recorded. Hemodynamic variables were also recorded at baseline (before the study drug infusion), after loading dose of study drug, before and after ketamine administration, and at 5, 10, 15, 30, 45 and 60 minutes after the procedure. It was also planned that if hypotension occurred (SBP < 80 mm Hg), the patients would be primarily treated with fluid administration (0.9% saline 10 mL kg^{-1}h^{-1}).

Patients were instructed on the use of Visual Analogous Scale (VAS) self-rating method. All patients used a separate 10-cm VAS device to assess the level of pain (0, no pain; 10, worst possible pain). Sedation was assessed on a five-point scale ('0' = no sedation—patient wide awake and alert; 4' = deep sleep, difficult to rouse). Pain and sedation were assessed by an assistant at 1, 2, 4, 6, 12 hours postoperatively.

A pain score <5 was considered adequate analgesia. As required to treat inadequate analgesia (e.g., increase in mean SBP, 25% above baseline; purposeful movements; swallowing; grimacing), the ketamine bolus (0.5-1 mg kg^{-1}) was given as a rescue analgesic. The total dose of ketamine used for rescue analgesia was also recorded. Sedoanalgesia time was recorded for all groups. Sedoanalgesia was defined primarily as VAS <5 and sedation scores >2.

During the study period, the number of patients requiring additional ketamine; and time to dressing change and recovery time for all patients were recorded. Incidence and severity of side effects (e.g., nausea, vomiting, hemodynamic events), if any, were recorded.

Qualitative data were analyzed with pearson Chi-square test. Quantitative data, expressed as 'mean ± standart deviation (SD)', were analyzed by one way ANOVA test. A probability value of .05 was considered statistically significant. All analyses were done by using statistical package for social sciences (SPSS) version 10.0 (SPSS, Chicago, IL).

Results

The characteristics of the 90 patients who completed the study are summarized in Table 1. Demographic characteristics (age, weight, sex), time to dressing change and recovery time were similar among the groups. SBP was significantly lower in group KD in comparison with the other groups at, before and after ketamine administration; and 5, 10 and 15 minutes after the procedure (P < .05) [Table 2]. Thereafter, there was no significant difference in SBP among the groups (data

Table 1: Demographic characteristics of patients in the study groups

	Group KD (*n*- = 30)	Group KM (*n*= 30)	Group KS (*n*= 30)
Age (years)	26.7 ± 6.1	25.0 ± 6.8	33.4 ± 18.9
Sex (M/F)	20/10	22/8	19/11
Weight (kg)	61.5 ± 7.6	65.2 ± 9.9	63.7 ± 6.5
Dressing changes time (min)	19.0 ± 9.1	22.8 ± 9.7	20.7 ± 4.6

Time to dressing change, age and weight values in the above table are in terms of 'mean ± SD'

Table 2: Systolic blood pressure in the study groups

	Group KD (*n* = 30)	Group KM (*n* = 30)	Group KS (*n* = 30)
Before infusion	140.9 ± 18.4	146.3 ± 16.1	138.2 ± 20.3
After infusion	141.7 ± 16.7	147.8 ± 17.9	143.8 ± 24.6
Before ketamine	135.4 ± 18.0*	149.8 ± 17.1	140.1 ± 22.0
After ketamine	137.9 ± 18.0*	157.1 ± 18.7	148.4 ± 24.5
After 5 min	137.5 ± 19.7*	161.2 ± 16.6	155.4 ± 23.2
After 10 min	137.7 ± 21.1*	162.2 ± 20.4	157.0 ± 29.8
After 15 min	139.0 ± 21.7*	164.2 ± 14.7	152.0 ± 18.7

*Note: Values in the above table are in terms of 'mean ± SD'. *P<0.05*

Table 3: Pain scores in the study groups

VAS	Group KD (*n* = 30)	Group KM (*n* = 30)	Group KS (*n* = 30)
1 h	2.1 ± 2.1	2.1 ± 2.0	1.4 ± 2.5
2 h	0.9 ± 1.8	1.0 ± 1.2	0.7 ± 1.6
4 h	0.2 ± 0.7	0.2 ± 0.5	0.2 ± 0.9
6 h	0.3 ± 0.1	0.0 ± 0.0	0.3 ± 1.0
12 h	0.0 ± 0.0	0.0 ± 0.3	0.1 ± 0.5

Note: Values in the above table are in terms of 'mean ± SD'

Table 4: Sedation scores in the study groups

	Group KD (*n* = 30)	Group KM (*n* = 30)	Group KS (*n* = 30)
1 h	1.8 ± 0.8*	1.2 ± 0.4	1.4 ± 0.6
2 h	1.1 ± 0.4	1.0 ± 0.10	1.0 ± 0.3
4 h	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.0
6 h	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
12 h	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0

*Note: Values in the above table are in terms of 'mean ± SD'. *P=0.001*

Table 5: Side effects in the study groups

	Group KD (*n* = 30)	Group KM (*n* = 30)	Group KS (*n* = 30)
Nausea and vomiting	-	2	-
Hypotension	1	-	-
Hypertension	-	-	-
Allergic rush	-	-	1
Hallucination	-	-	1

not shown in Table 2). No significant difference was found in DBP and HR among the groups.

There was no statistically significant difference in pain scores among the groups during the study period [Table 3]. At the first hour, sedation scores were higher in group KD than in group KM and KS. Sedation scores are shown in Table 4. The number of patients requiring additional ketamine was similar among the groups, and there was no significant difference. Duration of sedoanalgesia was significantly longer in group KD than in group KM ($P < 0.05$).

There were four adverse events in all the groups [Table 5]. A 23-year-old male patient who had received ketamine-dexmedetomidine combination experienced brief (<1 hour) episode of hypotension (SBP, 60 mm Hg), and it was treated mainly with IV fluid (0.9% saline infusion 10 mL kg^{-1} h^{-1}) administration. Two patients in group KM experienced nausea and vomiting. Only 1 patient among those who had received ketamine-saline combination experienced hallucination. Hypoxia and apnea were not observed in any of the study patients.

Discussion

In this study, we have demonstrated that three sedoanalgesic techniques provided effective sedation and analgesia during wound dressing changes in burn patients.

Burn care requires daily debridement, dressing changes and assessment regarding the need for skin grafting. These procedures are painful and may require an operating room environment. To increase the comfort of burn patients during dressing changes, it is necessary to give a patient tailored IV sedation with analgesic and anxiolytic drugs and to take into account the daily self-evaluation of the patient's pain.[1-4] The pain following burn injury is a complex mixture of background and incident pain with inflammatory and neuropathic components. Burn injury is among the most severe forms of trauma, and burn pain, in particular, is one of the most severe forms of acute pain, which necessitates aggressive use of opioids. Currently, narcotics such as morphine, meperidine and fentanyl are the most common forms of analgesic therapy in use for burn patients.[4] Nowadays ketamine and other analgesic drugs such as acetaminophen, NSAIDs (nonsteroidal anti-inflammatory drugs), local anesthetics, benzodiazepines, clonidine, nitrous oxide–oxygen mixtures; and psychological techniques are used.[3-11]

The effect of ketamine is thought to be the result of N-methyl-D-aspartate (NMDA) receptor antagonism, opioid l receptor agonism, and voltage-sensitive sodium channel interactions.[15,16] In humans, ketamine is agent for providing intraoperative and postoperative analgesia in burn patients. Humphries *et al.*[7]

used oral ketamine as an analgesic and sedative for wound-care procedures in children with burns, and demonstrated improved analgesia and sedation with oral ketamine compared with commonly used narcotics and sedatives. Owens *et al.*[8] used IV ketamine for painful procedures in pediatric burn patients. They found that, ketamine can be safely and effectively used for bedside procedures in pediatric burn patients. During dressing changes in burn patients, the major advantage of ketamine is that it usually preserves airway patency and respiratory function. In our study, ketamine did not result in any respiratory depression or apnea during the study period.

Dexmedetomidine is a recently developed α2-agonist that shows much greater selectivity for the 2-adrenoceptor than the other widely used agonists (e.g., clonidine).[12-14] It produces dose-dependent analgesia (involving spinal and supraspinal sites) without respiratory depression.[17] The analgesic profile of dexmedetomidine has not been fully characterized in humans. In a previous study, it was reported that clonidine counterbalanced the sympathetic stimulation of ketamine by virtue of its action in reducing sympathetic outflow, and the combination of clonidine and ketamine may be useful for burn patients with hypertension or myocardial ischemia.[18] In this study, counterbalance of the sympathetic stimulation by ketamine may have been provided by dexmedetomidine.

Midazolam provides sedation anxiolysis and less respiratory depression.[9-11] Walker *et al.*[19] compared dexmedetomidine infusion with standard sedation regimen of opioids and benzodiazepines in pediatric burn patients. They reported that with dexmedetomidine titration, all patients were rated "adequately sedate," even though all were sedation failures with opioids and benzodiazepines.

To our knowledge, this is the first study comparing the sedoanalgesic effects of ketamine, ketamine-dexmedetomidine combination and ketamine-midazolam combination during wound dressing changes in burn patients. Previous studies have reported attenuation of hypertension and tachycardia in response to laryngoscopy and intubation by dexmedetomidine.[20] Hemodynamic responses may be seen during dressing changes in burn patients, and they are not as frequent and profound as those seen with intubation or laryngoscopy. Hemodynamic events seen during dressing changes may be related with either plasma concentration of catecholamines or study drugs. In our study, there was no greatly significant difference between the groups in hemodynamic parameters, except that systolic blood pressure was significantly lower in the KD group than in KM and KS groups at the first hour. The changes in HR and DBP were similar for the treatment groups. Talke *et al.*[21] reported that dexmedetomidine (plasma concentrations in the range of 0.18 to 0.35 ng/mL) attenuates the increases in HR and plasma norepinephrine concentrations observed during emergence from anesthesia. Furthermore, it has also been reported that dexmedetomidine attenuates the hyperadrenergic state associated with ketamine. We did not measure either norepinephrine or dexmedetomidine plasma concentrations. Therefore, we failed to demonstrate any correlation between hemodynamic variables and plasma catecholamine concentrations.

The most frequently seen adverse effect of ketamine is emergence of reactions or hallucinations. Recovery agitation of ketamine has been modestly associated with decreasing age and the presence of an underlying medical condition.[22] In this study, only 1 patient among those who had received only ketamine-saline combination experienced hallucination. Owens *et al.*[8] reported that 2.9% of the patients who received ketamine during sedation experienced side effects such as desaturation, apnea, hypotension. Walker *et al.*[18] stated that no respiratory depression associated with the use of dexmedetomidine had occurred. Similarly, in a recent study, Taghinia *et al.*[23] reported that dexmedetomidine decreased the frequency of oxygen desaturation and reduced the amounts of narcotic and anxiolytic requirement. In this study, we did not observe any respiratory depression, hypoxia or apnea in any group. Hemodynamic variables were also similar among the groups in each study period, except SBP was significantly lower in group KD than in groups KM and KS at the first hour. The most frequently seen adverse effects of IV dexmedetomidine that have been reported are hypotension and bradycardia.[24] In this study, only a brief episode (<1 hour) of hypotension (SBP, 60 mm Hg) was observed in a 23-year-old male patient who had received ketamine-dexmedetomidine combination, and it was treated mainly with IV fluid (0.9% saline 5-10 mL $kg^{-1} h^{-1}$) administration.

Although midazolam and dexmedetomidine are known as sedative agents, sedation scores were significantly higher in group KD than in group KM following the first hour of the study period. Dexmedetomidine has been reported to be associated with a long-arousable sedation, and this could be the reason why sedation scores were significantly higher in the KD group than in KM and KS groups.[17]

Green *et al.*[22] reported that the incidence of emesis after ketamine administration was modestly associated with increasing age. Ünlügenç *et al.*[25] reported that the sedative effects of midazolam and propofol lasted for a much shorter time than the antiemetic effects of these drugs, and these drugs used in subhypnotic doses were as effective as ondansetron in treating PONV (postoperative nausea and vomiting) in patients undergoing abdominal or gynecological surgery. In this study, nausea and vomiting were observed in 2 patients

in group KM. Lower incidence of emesis in KD group was thought to be associated with the use of dexmedetomidine. Taghinia *et al.*[23] have reported that dexmedetomidine decreased antiemetic use.

In conclusion; in burn patients undergoing dressing changes, although both combinations, viz., ketamine-dexmedetomidine and ketamine-midazolam, offered effective sedoanalgesia without causing any significant side effects, the former resulted in higher sedation and lower hemodynamic discrepancy.

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