Oral ketamine for wound care procedures in adult patients with burns

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Abstract

Background: This prospective study was carried out to evaluate the usefulness of oral ketamine for burn wound dressing in adult patients. The aim was to achieve a state-of-conscious sedation in which the patient would be communicative and cooperative, with minimal, or no pain during burn wound care procedures.

Method: Two hundred and forty wound care procedures were randomly assigned to six treatment groups of patients (groups A-F). The quantities of oral ketamine that they received were as follows: Group A, 0.5 mg/kg; B, 2 mg/kg; C, 4 mg/kg; D, 6 mg/kg; E, 8 mg/kg and F, 10 mg/kg. A five-point verbal rating scale was used to assess pain intensity: the AVPU (alert, voice, pain, unresponsive) scale for level of consciousness. The Likert scale was used for patient satisfaction. Blood pressure, pulse rate and oxygen saturation were monitored. Adverse effects were noted. Comparisons of the efficacy and safety of the different dosages of oral ketamine were made using the SPSS package. The efficacy criterion was verbal rating scale (VRS) ≤ 2, i.e no pain, mild pain or discomfort.

Results: Patients in groups A and B reported higher levels of pain, and in groups C, D, E and F, there were varying degrees of efficacy. Groups E and F had the best analgesic profiles, but at the higher doses, some patients became anaesthetised. The most common adverse effects reported were hallucination (37%) and hypersalivation (29.9%), which occurred more frequently in groups E and F. The patients' assessments of pain were best in Group D, and worst in Group A.

Conclusion: The minimum effective subanaesthetic dose of oral ketamine for analgesia during wound care procedures in adult patients with burns was 6 mg/kg.

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Introduction

Ketamine, an N-methyl-D-aspartate antagonist, is known to have very potent analgesic properties when given at subanaesthetic doses.[1] Traditionally, it has been used parenterally, although it is well absorbed orally,[2] nasally and rectally. Oral ketamine is effective in the treatment of severe complex regional pain syndrome type 1,[3] central post-stroke pain, and multiple sclerosis with severe pain and allodynia.[4] The use of oral ketamine for pain relief has also been described for post-amputation stump pain, post-herpetic neuralgia, phantom limb pain, neuropathic pain and cancer pain.[5,6]

Burns, defined as coagulative necrosis of the skin, can occur as a result of exposure to thermal stimuli such as flames, hot metal or liquids, electricity, chemicals or radiation. These produce tissue damage, leading to acute inflammation and hyperalgesia with consequent pain. This pain is worsened by the need to change dressings frequently in order to prevent infection and aid healing.[7] Burn injuries that expose painful nerve endings in the superficial layer of the dermis are the most painful. Therefore, adequate pain relief during such wound care procedures is highly desirable, especially if achieved via an atraumatic route.

Ketamine in subanaesthetic doses has been shown to reduce both primary and secondary hyperalgesia in burns patients. Humphries et al[8] found that oral ketamine is superior to acetaminophen with codeine phosphate and diphenhydramine for wound care procedures in paediatric patients with burns.

The aims of this study were to evaluate the effectiveness of oral ketamine as an analgesic for wound care procedures in adult patients with burns, and to establish possible adverse effects and the minimum effective subanaesthetic dose of oral ketamine during wound care procedures in such patients.

Method

This prospective, non-placebo, single-blind, randomised comparative study was carried out in adult patients with burns over a period of one year at the Burns Unit, National Orthopaedic Hospital, Enugu, in south-east Nigeria.

Approval of the Research and Ethics Committee of the National Orthopaedic Hospital, Enugu, and the informed consent of each patient were obtained. Inclusion criteria were all consenting adult patients with severe burns pain, being treated with regular dressings. Exclusion criteria were patients with hypertension, ischaemic heart disease, cerebrovascular accident, raised intracranial pressure, hyperthyroidism, critically ill patients with American Society of Anesthesiologists' (ASA) physical status ≥ 3, and deaf and dumb patients. Patients with extensive burns involving the upper extremities, with no place for the attachment of blood pressure apparatus or pulse oximeter probes, were also excluded.

All adult patients who satisfied the criteria were randomly assigned to each of the six treatment groups (A: 0.5 mg/kg ketamine, B: 2 mg/kg, C: 4 mg/kg, D: 6 mg/kg, E: 8 mg/kg, F: 10 mg/kg). Each dressing session on a patient was subjected to random sampling in order to be assigned to a treatment group. Data collection was obtained through completion of a questionnaire specifically designed for the study. Two hundred and forty questionnaires were prepared. Patients were randomly assigned to the six treatment groups, using a coded numbering system comprising a serial number, treatment group and dose of oral ketamine; e.g, code no 1A0.5 meant serial number 1, treatment group A and an oral ketamine dose of 0.5 mg/kg. This was decoded to the pharmacists only, to enable them to compound the dose of ketamine for each treatment group. Injectable ketamine (50 mg/ml), manufactured by Claŕis Lifesciences Limited, was diluted to a strength of 10 mg/ml with bottled/sachet water and 0.5 g/ml of Allenburys Glucose D to mask the bitter taste of ketamine. The different dosages were then measured and dispensed to patients according to their weight and dosage groups.

Burns dressing procedures were carried out in the wards, early enough in the morning to reduce fasting time, as all patients were required to fast overnight, or for at least six hours. The patients were premedicated with oral diazepam 0.15 mg/kg 90 minutes prior to the oral ketamine administration. No antisialogogue was given. Equipment for cardiopulmonary resuscitation (ambu bag, laryngoscope, endotracheal tube, suction catheters, oxygen source and emergency drugs) were made available in all cases.

Each patient's weight, height, pre-ketamine blood pressure [systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP)], pulse rate and oxygen saturation was recorded. Dressing commenced 20 minutes after taking the medication, or when the verbal rating scale (VRS) score was ≤ 2, whichever was earlier. In patients with severe burns, more than one nurse was asked to dress the wound in order to reduce the dressing time. Rescue analgesia (intravenous ketamine 1 mg/kg and glycopyrrolate 5 µg/kg) was given to any patient still experiencing pain or breakthrough pain during the procedure, following which that particular session was dropped from the study.

Anaesthetists were trained to interview the patients while completing the questionnaires. Only the patients were blinded to the dose of oral ketamine received. Pain assessment was based on self-report (patient's own experience). It was either carried out during the procedure for conscious patients, or on completion of the procedure for anaesthetised patients, using the VRS (see Table I).

Table I: VRS, AVPU and Likert scales used to assess degree of satisfaction

Score	[a]VRS scale	Score	[b]AVPU scale	Score	Likert scale
0	No pain	-		0	Very dissatisfied
1	Mild pain	1	Alert	1	Dissatisfied
2	Discomfort	2	Response to voice	2	Slightly dissatisfied
3	Distressing	3	Response to pain	3	Slightly satisfied
4	Horrible	4	Unresponsive	4	Satisfied
5	Excruciating	-		5	Very satisfied

a = verbal rating scale; b = alert, voice, pain, unresponsive scale for level of consciousness

The efficacy criterion was VRS ≤ 2, and "significant change" referred to reduced pain intensity felt during dressing, in a range from VRS ≥ 3 to VRS ≤ 2. Automated non-invasive blood pressure monitoring and pulse oximetry were recorded at five-minute intervals for at least two hours. The alert, response to voice, response to pain, unresponsiveness (AVPU) scale was used to assess the level of consciousness needed to determine the subanaesthetic dose of oral ketamine (see Table I). The subanaesthetic dose of oral ketamine was that which produced a sedation score of ≤ 3.

Each patient's level of satisfaction with pain management was evaluated using a six-point Likert scale (see Table I). Assessment of safety was determined using level of consciousness and occurrence of side-effects reported

during and after the procedure, such as hallucination, nausea, vomiting and hypersalivation.

Data analysis

The data collected in this study were subjected to statistical analysis using the computer-based statistical software package SPSS, version 13. Means and standard deviations were computed for all dependent variables. Analysis of variance (ANOVA) was used to compare the means and standard deviation of demographic characteristics of the six treatment groups. Efficacy of the various doses of oral ketamine for pain relief was determined using the chi-square statistical test of significance. Comparisons of various categorical variables such as pain intensity, level of consciousness and adverse side-effects, as well as continuous variables such as blood pressures and heart rate, were analysed with one-way ANOVA. The null hypothesis was rejected at p-values < 0.05.

Results

A total of 240 wound care procedures were carried out in 51 patients: 28 males (54.9%) and 23 females (45.1%). Forty procedures were performed in each of the treatment groups (A-F). The number of procedures carried out on a patient ranged from one to nine, with a minimum interval of 48 hours. The demographic characteristics of the six treatment groups are presented in Table II. There was no statistically significant difference between the six treatment groups in age, p-value = 0.907; sex, p-value = 0.843; and body mass index, p-value = 0.941.

Assessment of procedural pain using VRS in the six treatment groups is shown in Figure 1. The comparison of pain rating among the treatment groups was statistically

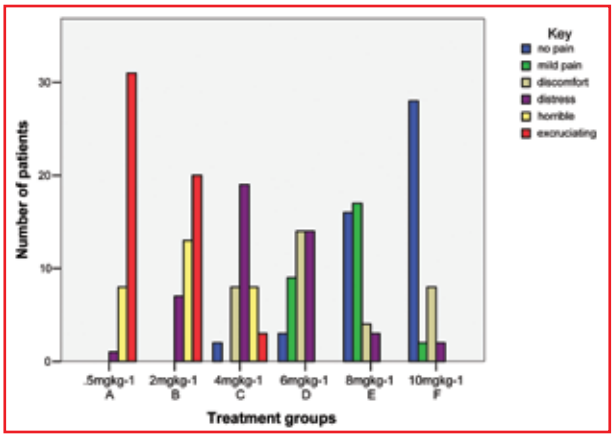

Figure 1: Comparison of VRS between the treatment groups

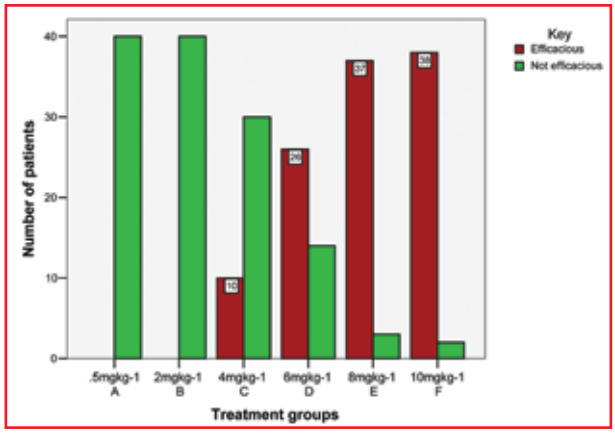

Figure 2: Comparison of efficacy of oral ketamine between the treatment groups

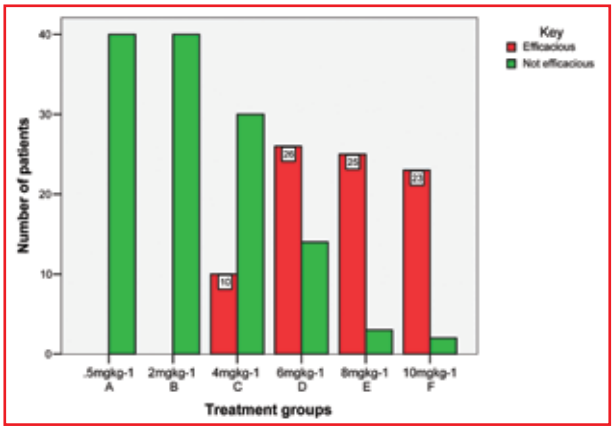

Figure 3: Comparison of efficacy of oral ketamine between the treatment groups in the conscious patients

Table II: Comparison of demographic characteristics between the six treatment groups (A–F)

	Group A 0.5 mg/kg	Group B 2 mg/kg	Group C 4 mg/kg	Group D 6 mg/kg	Group E 8 mg/kg	Group F 10 mg/kg	Total	P-value
Number of patients	40	40	40	40	40	40	240	
Mean age (years) (± [a]SD)	34.3 (± 12.3)	36.1 (± 1.6)	35.3 (± 9.5)	36.5 (± 10.5)	37.9 (± 4.5)	35.2 (± 13.5)	36.0 (±13.8)	0.907
Male Female	20 (50%) 20 (50%)	26 (65%) 14 (35)	22 (55%) 18 (45%)	23 (57.5%) 17 (42.5%)	22 (55%) 18 (45%)	21 (52.5%) 18 (45%)	134 (55.8%) 106 (44.2%)	0.843
Mean weight (kg) (± SD)	56.1 (± 6.3)	56.6 (± 5.3)	56.9 (± 5.5)	56.6 (± 5.7)	57.1 (± 5.9)	56.6 (± 5.2)	56.7 (± 5.6)	0.767
Mean body mass index (kg/m^2) (± SD)	22.8 (± 2.4)	22.8 (± 2.4)	23.1 (±2.6)	23 (± 2.5)	23.3 (± 2.9)	22.8 (± 2.1)	23 (± 2.5)	0.941

a = standard deviation

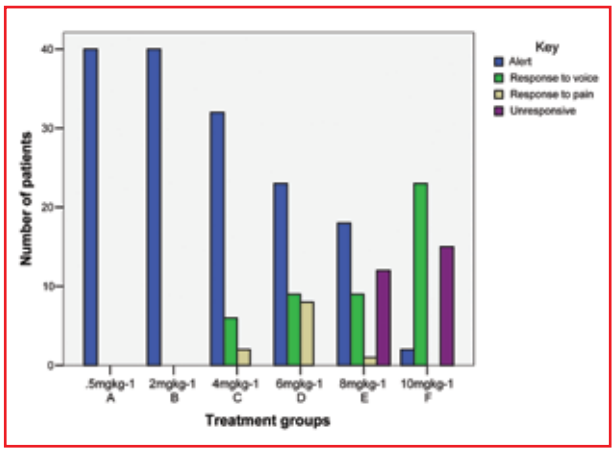

Figure 4: Comparison of level of consciousness between the treatment groups

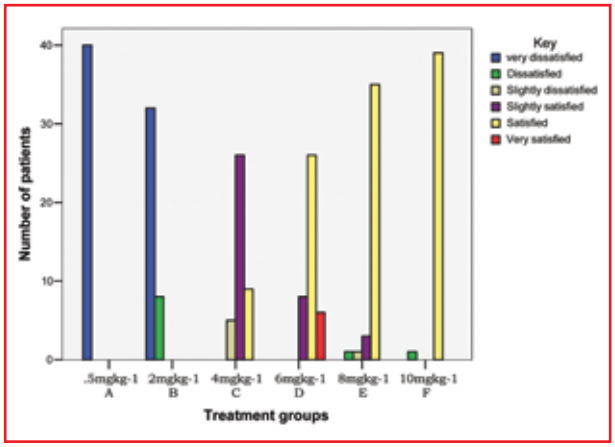

Figure 5: Comparison of patients' satisfaction assessment between the treatment groups

significant (p-value = 0.000). Efficacy of oral ketamine in the different groups is shown in Figure 2. In Figure 3, the efficacy of oral ketamine in conscious patients only is compared. Group D had the highest score: 26 (65%). The minimum effective subanaesthetic dose of oral ketamine was therefore 6 mg/kg. Comparison of the efficacy of oral ketamine within the treatment groups was statistically significant (p-value = 0.000). Assessment of sedation using the AVPU scale is shown in Figure 4. The comparison of the level of consciousness among the treatment groups was found to be statistically significant (p-value = 0.000). Assessment of patients' satisfaction with oral ketamine is shown in Figure 5. The comparison of patients' satisfaction with oral ketamine among the six treatment groups was statistically significant (p-value = 0.000).The incidence of side-effects reported among the treatment groups is shown in Table III. Comparison of adverse effects among the treatment groups was statistically significant (p-value = 0.000). The magnitude of variation in haemodynamic variables is shown in Table IV. The results of haemodynamic monitoring showed a statistically significant increase in haemodynamic variables in all the groups (p-value = 0.000). The mean percentage increase in SBP, DBP, MBP and heart rate (HR) was higher in treatment groups F and E, and lower in treatment groups D, C, B and A. Comparisons of haemodynamic parameters among the treatment groups were statistically significant (p-value = 0.01). There was no recorded desaturation of less than 90% in any group.

Table III: Comparison of adverse/side effects between the six treatment groups (A–F)

Side-effects	Group A 0.5 mg/kg	Group B 2 mg/kg	Group C 4 mg/kg	Group D 6 mg/kg	Group E 8 mg/kg	Group F 10 mg/kg	Total	P-value
Hallucination	0 (0%)	0 (0%)	4 (10.0%)	6 (15.0%)	15 (37.5%)	22 (55.0%)	47 (37.01%)	0.000
Hypersalivation	0 (0%)	0 (0%)	7 (17.5%)	8 (20.0%)	11 (27.5%)	13 (32.5%)	39 (29.92%)	0.000
Dizziness	4 (10.0%)	3 (7.5%)	4 (10.0%)	2 (5.0%)	7 (17.5%)	1 (2.5%)	21 (16.54%)	0.241
Nausea and vomiting	3 (7.5%)	0 (0%)	1 (2.5%)	2 (5.0%)	0 (0%)	0 (.0%)	6 (4.72%)	0.145
Headache	8 (20.0%)	6 (15.0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.5%)	15 (11.81%)	0.000
Total	15 (11.72%)	9 (7.03%)	16 (12.5%)	18(14.06%)	33 (25.78%)	37 (28.91%)	128 (100.0%)	0.001

Table IV: Mean percentage increase in haemodynamic variables 30-minutes post-oral ketamine administration in six treatment groups (A-F)

Haemodynamic variables (as percentages)	Group A 0.5 mg/kg	Group B 2 mg/kg	Group C 4 mg/kg	Group D 6 mg/kg	Group E 8 mg/kg	Group F 10 mg/kg
Systolic blood pressure	20.0	13.3	10.8	16.7	26.6	32.5
Diastolic blood pressure	32.9	25.7	18.1	22.2	34.7	35.6
Mean blood pressure	27.2	19.8	17.6	22.1	32.2	36.4
Heart rate	35.5	34.8	31.6	32.9	47.8	49.6

P-value = 0.01

Discussion

An ideal analgesic agent for burn wound care procedures should possess some positive attributes, such as the provision of adequate pain relief via an acceptable atraumatic route of administration, a wide safety margin, rapid and reliable onset, rapid elimination, and suitability for long-term use. It should not cause cardiopulmonary depression, and should confer haemodynamic stability with no effects on the liver and kidneys. The drug should have no tolerance or addictive properties, and be suitable for use in non-intensive care unit or operating room settings.

Results of this study showed that, at 6 mg/kg of oral ketamine, 65% of adult patients with burns experienced adequate pain relief and exhibited full cooperation during burn wound dressing. The criterion for the efficacy of oral ketamine at subanaesthetic doses is the provision of adequate analgesia without anaesthesia. An anaesthetised adult burns patient who cannot obey commands, or a patient in severe pain, would make the execution of dressing procedures cumbersome. This may lead to inadequate wound care and consequent complications such as sepsis, a longer hospital stay, and an increase in morbidity or mortality.

Ethical issues were considered in the selection of the study design. A comparative, non-placebo (no control) design was adopted to avoid the issue of denying a burns patient the potential benefits of oral ketamine analgesia, and crossing of patients within the treatment groups, permitted by random sampling, allowed each patient to act as his or her own control.

Oral ketamine at a dose of 0.5-2 mg/kg (groups A and B) was not efficacious. This is contrary to the results of the study carried out among adult chronic neuropathic pain patients by Furuhashi-Yonaha et al.[5] In their study, the severity of pain and allodynia was reduced by oral ketamine 0.5 mg/kg 15 minutes after administration, and improvement lasted for six to eight hours. In this study, the degree of burns pain was so high that oral ketamine 0.5-2 mg/kg was 100% inefficacious, and so should not be prescribed for procedural burn pain.

The efficacies of oral ketamine at the various doses were as follows: group C: 4 mg/kg (25%); group D: 6 mg/kg (65%); group E: 8 mg/kg (92.5%) and group F: 10 mg/kg (95%), indicating that the analgesic efficacy of oral ketamine is dose-dependent. In group D, there was a greater percentage of efficacy than in group C (65% versus 25%). Although oral ketamine 8-10 mg/kg provided more effective analgesia, it was found to be unsafe, because 30-37.5% of patients were anaesthetised. Burn wound dressings are usually bedside procedures and general anaesthesia in such a non-intensive care unit or operating room setting would simply be unsafe, in spite of the availability of resuscitative equipment, monitoring devices and emergency drugs.

Paediatric patients are known to be uncooperative while awake. Consequently, several researchers found a dose of 10 mg/kg ideal in children undergoing painful procedures. Raghu Raman and Deshmukh[9] found that, in a dose of 10 mg/kg, oral ketamine gave an ideal combination of good sedation with minimal emergence phenomenon for a child undergoing an invasive diagnostic or therapeutic procedure. In our study, five per cent of patients still had distressing pain even after receiving 10 mg/kg oral ketamine. This can be attributed to interindividual differences such as personality, psychology, ethnicity, and social and medical factors affecting pain perception.

The incidence of psychic disturbances following ketamine administration is known to be greater in adults than in children. Reported disturbances include alterations in mood and body image, floating sensations, dissociative experiences, vivid dreams or illusions, and delirium. There is a paucity of published work relating dosages to the adverse effects of oral ketamine in adult patients. Most studies have been conducted on paediatric patients. In this study, the result of adverse side-effects of oral ketamine were found to be dose related, unlike in the study carried out by Raghu Raman and Deshmukhl[9] in paediatric patients, where the incidence of emergence phenomenon was 8% in paediatric patients receiving 6 mg/kg, and 12% in those receiving 10 mg/kg, with no statistically significant difference (p-value > 0.05). The incidence of hallucination in our adult patients receiving 6 mg/kg was 15%, compared to 55% in those receiving 10 mg/kg of ketamine (p-value = 0.000), despite premedication with oral diazepam 0.15 mg/kg. Oral midazolam, which was not available to us at the time of the study, has been found to have better effect than diazepam when taken in combination with oral ketamine.[10,11]

The incidence of hypersalivation in adult patients receiving 4-10 mg/kg was 17.5-32.5%. The study of Gutstein et al[12] on oral ketamine in paediatric patients, in which 3-6 mg/kg was used, showed that increased salivation occurred in 13-33% of cases. No anticholinergic agent was used as premedication in the above study, as in other similar studies with oral ketamine. According to Raghu Raman and Deshmukh,[9] "oral atropine imparts a bitter taste". Time-to-peak decrease in salivation is two hours, significantly slower than the time to peak ketamine effect. The intramuscular route defeats the purpose of avoiding an injection. The 17.5-20% of patients who received 4-6 mg/kg ketamine had hypersecretion, but remained capable of clearing their

airways, indicating that oral atropine pre-treatment was unnecessary. The protective airway reflexes were intact, reducing the risk of pulmonary aspiration. The study of Cem et al[13] showed that oral ketamine is still safe without concurrent atropine administration.

Hypersalivation, which may predispose an anaesthetised patient to laryngospasm, was reported in 27.5-32.5% of patients in groups E and F respectively. Precautionary airway management with oropharyngeal suctioning was employed to minimise this risk. No patient had laryngospasm in our study.

Ketamine increases blood pressure and heart rate due to sympathetic stimulation. However, a subanaesthetic dose of oral ketamine has been associated with minimal or no haemodynamic disturbances.[14] Results of this study showed a higher increase in haemodynamic parameters in patients receiving 8-10 mg/kg in comparison to patients receiving 4-6 mg/kg (the subanaesthetic dose). This implies less risk of cardiovascular complications for patients receiving 4-6 mg/kg, compared to a dose of 8-10 mg/kg.

The patients' assessment of satisfaction profile is in agreement with results of a study done by Carrougher et al.[15] Patients with the highest levels of procedural pain reported the lowest levels of satisfaction, as in patients in groups A and B. Patients who were previously dissatisfied with a dose of 0.5 mg/kg were satisfied with a higher dose (≥ 6 mg/kg). Groups F and E, who recorded better pain scores, still had some degree of dissatisfaction because of unconsciousness (anaesthesia) and hallucination. In a study done by Enarson et al[16] on 21 patients, nine (42.5%) discontinued oral ketamine because of intolerable side-effects. In addition, orally administered injectable ketamine still left an unpleasant bitter taste, despite the addition of glucose.

There has been major concern about the development of tolerance and the physiological or psychiatric effects of using oral ketamine frequently for a prolonged period of time, as demanded by burn wound dressings. In the early days of ketamine use, Bjarusen and Corssen[17] noted evidence of tolerance when more than eight doses of ketamine were administered. Bennett and Bullimore[18] similarly noted that in their series, seven out of 10 children who received ketamine developed tolerance. Pouget et al,[19] using macaque monkeys in their oculomotor study, demonstrated rapid development of tolerance to subanaesthetic doses of ketamine. On the other hand, results of Cvrekr's[14] study on the long-term side-effects of oral ketamine were in agreement with those of Furuhashi-Yonaha et al,[5] who did not observe serious adverse effects or tolerance to subanaesthetic doses of oral ketamine. No noticeable evidence of tolerance to ketamine was seen in our study. The Yale Ketamine Study Group[20] showed the psychiatric safety of ketamine, while Cho et al[21] demonstrated the absence of behavioural sensitisation in healthy subjects following repeated exposure to ketamine. In our study, no patient was reported to have had any serious adverse effects.

It was difficult to compare results from other studies on pain relief with oral ketamine in adult burn patients because at present, there is no published work in this area. A comparison was made between 6 mg/kg of oral ketamine and intravenous short-acting, potent opioids agonists (remifentanil, alfentanil and fentanyl), the cornerstone of procedural burns pain management.[22] Oral ketamine is at a major disadvantage with delayed onset of action (20 minutes), which does not allow for analgesic therapy to be easily adjusted in order to meet individual needs. On the other hand, intravenous opioids need to be administered in an anaesthesiology environment[23] with monitoring and resuscitative equipment. Sophisticated devices and well-trained staff are also required to reduce the risk of apnoea due to respiratory depression and loss of consciousness. Oral ketamine, with its acceptable atraumatic route of administration, has a place in developing countries where the abovementioned equipment and manpower are lacking.[24-25]

There is still a need to achieve a completely "pain-free state". With a dose of 6 mg/kg, oral ketamine provided analgesia in only 65% of patients. Increasing the dose further increases the analgesic effect, but with the risk of anaesthetising the patients and increasing the side-effects. There is evidence that patients benefit from the use of a multimodal, or balanced, analgesia approach in acute pain management.[26] Oral paracetamol, other non-opioid analgesics and opioids can be employed in combination with 6 mg/kg oral ketamine to improve pain relief, with a reduction in the incidence and severity of side-effects. Exploring the benefits of a multimodal approach for burn wound dressing procedures that combine 6 mg/kg of oral ketamine with other oral analgesics for improved analgesia, needs to be addressed in further clinical studies.

Conclusion

To be effective, the minimum subanaesthetic dose of oral ketamine for wound care procedures is 6 mg/kg. At this dose, 65% of patients experienced adequate pain relief and demonstrated full cooperation during burn wound dressing. Wound dressing should begin 20 minutes after administration of oral ketamine (onset of action is 20 minutes) and should conclude within 20 minutes. Increasing the dose further increases the analgesic effect, with the risk of anaesthetising the patients and increasing the side-effects such as hallucination hypersalivation, nausea, vomiting, and a further increase in blood pressure, dizziness and headache.

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