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## A comparison of analgesia requirements in children with burns: Do delayed referrals require higher procedural analgesia doses?

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### Abstract

**Background:** Our clinical impression is that delayed referrals require more analgesia than children referred to our service acutely. Previous work demonstrated poor uptake of analgesia protocols at district hospitals with probable inadequate background and procedural analgesia, which may account for this. The purpose of this study was to compare analgesia requirements for dressing changes of paediatric patients referred to us acutely versus those children with delayed referral (i.e. more than 21 days post injury). Our hypothesis is that paediatric patients with delayed referral require higher doses of ketamine when taking length of stay and total body surface area (TBSA) of the burn into account.

**Methods:** Data for children under 12 years, admitted to the Pietermaritzburg Burn Service (PBS) from the 1 July 2017 until 30 June 2018 was reviewed. Total ketamine dose during admission, weight, days admitted and TBSA were analysed. The total ketamine use in milligram per kilogram per days admitted per TBSA (mg/kg/days admitted/TBSA) was calculated. Statistical analysis was performed to compare the total ketamine dose between the acute and delayed referral groups.

**Results:** One-hundred-and-ninety-seven patients were included. Patients were divided into two groups, the acute group including those referred to the PBS early (prior to 21 days post-burn) and the delayed referral group (those referred 21 days or more post burn). The acute group consisted of 167 patients and the chronic group 30 patients. There is a statistically significant difference between the total ketamine dose (mg/kg/days admitted/TBSA) for the acute referral and delayed referral groups ( $p = 0.01$ ). The median total ketamine dose (mg/kg/days admitted/TBSA) of the acute referral group was 0.27 (Range: 0–7.05) and the median total Ketamine dose (mg/kg/days admitted/TBSA) for the delayed referral group was 0.41 (range: 0.1–3.89).

**Conclusion:** Patients with delayed referrals require more ketamine to achieve adequate procedural analgesia than patients referred acutely. Inadequate analgesia in the acute phase of

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<sup>7</sup>-Patient consent

The data for the paper was drawn from an existing database. We do get consent from all patients to store their data on the database.

Conflict of interest

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

the burn may influence this, underpinning the importance of adequate analgesia right from the time of the injury.

## Keywords

Burns; Analgesia; Pain; Delayed referral; Paediatric burns

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## 1. Introduction

Globally, pain control in burns patients remains inadequate despite longstanding recognition that inadequate pain control can have adverse physiological and emotional sequelae [1–4]. Inadequate analgesia as background as well as procedural, can contribute to the development of anxiety, wind up, allodynia and hyperalgesia [5]. It is difficult to distinguish each syndrome clinically, as they can all be perceived as acute somatic pain during a dressing change and in our practice, this equates to giving more procedural analgesia. Further, the dissociative effect of ketamine can also be perceived as pain by the inexperienced doctor. Ongoing inadequate background analgesia may also contribute to the development of neuropathic pain. This also perpetuates the escalation of procedural analgesia requirements.

Our clinical impression is that children with burn wounds managed at district hospitals for a number of weeks initially, require higher procedural analgesia doses compared to those that have been more acutely admitted to our service. Our previous work demonstrating poor uptake of analgesia protocols at these district hospitals with the potential development of complex pain syndromes is one explanation for our impression due to the probable inadequate background analgesia as well as procedural analgesia [6]. The purpose of this study was to compare the analgesia requirements for dressing changes of paediatric patients between acute referrals and delayed referrals, where delayed is defined as a burn wound that was referred more than 21 days from time of burn. Our hypothesis for this study was that burn-injured paediatric patients with delayed referral require higher doses of ketamine when taking length of stay and total body surface area of the burn into account.

## 2. Setting

The city of Pietermaritzburg is the largest city in western Kwa Zulu Natal Province. It has a population of a million people and drains the rural western third of the Province. The Pietermaritzburg Burn Service (PBS) consists of two burns surgeons who operate across the regional (Edendale Hospital) and Tertiary (Greys Hospital) Hospitals of Pietermaritzburg. The Burn Service has access to 40 beds dedicated burns beds. Ten beds are at Greys Hospital and the remaining thirty beds, including six high care beds, are at Edendale Hospital. Annually the patient load of the PBS consists of 500–600 inpatients (adults and children). Exclusive outpatient care is provided to a further 500 patients (adults and children). There are 19 rural district hospitals which the PBS supports. All patients treated by the PBS are entered onto a burns database. This has class approval granted by the Biomedical Research and Ethics Committee, University of Kwa-Zulu Natal (BCA106/14).

In our service, a combination ketamine and midazolam is administered to all children undergoing dressing changes in both the in-patient and out-patient setting. In-patients

receive the ketamine for their dressings in the ward where minimal monitoring equipment (saturation and heart rate) is available. A doctor is present for every dressing change, both to administer the ketamine and to monitor for adequacy of analgesia and to provide additional doses of ketamine as required. The patient is given an initial dose of ketamine, should the analgesia be inadequate an additional dose of ketamine is given. For the next dressing change, the total ketamine dose given at the previous dressing change (the initial dose plus the additional dose) is given as the initial dose of ketamine. This may, however, lead to rapidly escalating doses of ketamine being administered. Only the ketamine can be given as a repeat dose and midazolam remains as a single dose given with first dose of ketamine. Patients are discharged when the wounds are healing, are unlikely to require any further surgery and when they are satisfactorily compliant with mobilization and or splinting.

### 3. Methods

Analgesia for dressings was prescribed as per out analgesia protocol (Appendix 1). In-patients received oral ketamine and midazolam 30 min prior to the procedure with an additional intramuscular dose of ketamine should adequate analgesia not have been achieved. The additional dose was given at half of the initial oral dose. Pain scores were recorded using the Face, Legs, Activity, Cry, Consolability (FLACC) scale to assess adequacy of analgesia [7]. If the initial dose of ketamine was insufficient to achieve adequate analgesia, the initial dose plus the additional doses are prescribed as the initial dose for the next dressing change. The protocols are adhered to for every dressing change.

Data regarding the total ketamine dose for the duration of the patient's admission is routinely collected as part of the burns data base. This study focused only on children who were admitted as in-patients to our service receiving ketamine only for procedural analgesia and not background analgesia. Data for children (<12 years old) admitted to the PBS from the 1 July 2017 until 30 June 2018 was reviewed. Age, admission weight and total ketamine dose were analysed. The date of admission and date of discharge were used to calculate the days admitted and the date and time of burn and the date and time of admission were used to calculate the delay from time of burn to admission. Children who were admitted to paediatric intensive care unit at any time during their admission were excluded as ketamine is used as an infusion for background analgesia. Children who demised during admission were excluded from the study as well as children with missing data on the database.

The patients were divided into two groups, those referred to the PBS early (prior to 21 days post-burn) and those with a delayed referral (those referred 21 days or more post burn). The total ketamine use in milligram per kilogram per days admitted per TBSA (mg/kg/days admitted/TBSA) was calculated. Statistical analysis was then performed using R Studio Version 1.1.463 [8]. A Mann-Whitney-Wilcoxon test was conducted to compare the acute referral and the delayed referral groups. A Fisher's exact test was then conducted to determine whether the total ketamine dose (mg/kg/days admitted/TBSA) was affected by mechanism of injury. A Fisher's exact test was also conducted to assess whether TBSA played a role in the total ketamine dose (mg/kg/days admitted/TBSA).

## 4. Results

There were 275 children admitted during the 1 year period under review. One-hundred-and-ninety-seven children met the inclusion criteria. Data for these children was evaluated. The patients referred early consisted of 167 patients and those with a delayed referral were 30 patients. The two groups are described in Table 1.

The mean delay from burn to admission in the late referral group was 48.2 days with a range of 21–230 days delay and a median of 29.5 days. The early referral group of patients presented from scene within an hour of the burn up to 19 days post burn injury.

A Mann-Whitney-Wilcoxon Test was performed to compare the total ketamine (mg/kg) per days admitted per TBSA. There was a statistically significant difference ( $W = 1778.5$ ,  $p = 0.01$ ) between the acute referral and delayed referral groups. The median total ketamine dose (mg/kg/days admitted/TBSA) of the acute referral group was 0.27 (range: 0–7.05) and the median total Ketamine dose (mg/kg/days admitted/TBSA) for the delayed referral group was 0.41 (range: 0.1–3.89). The comparison between the total ketamine doses between the acute and delayed referral groups can be seen in the boxplots in Fig. 1.

In order to determine whether mechanism of injury played a role in the total ketamine dose required, a two-sided Fisher's exact test was conducted for each of the groups. This test revealed that in the acute group there was a statistically significant difference in the total ketamine dose (mg/kg/days admitted/TBSA) required, depending on the mechanism of injury ( $p = 0.003$ , Fisher's exact test). However, in the delayed referral group, when considering mechanism of injury, the difference in total ketamine dose required was not statistically significant ( $p = 0.15$ , Fisher's exact test). In both the acute and delayed referral groups the electrical injuries required more than double the total ketamine dose than the other mechanisms of injury. Figs. 2 and 3 show the comparison of the total ketamine doses between the different mechanisms of injury for the acute and delayed groups respectively.

Statistical analysis using a two-sided Fisher's exact test confirmed that in the acute group there was a statistically significant difference in total ketamine dose (mg/kg/days admitted/TBSA) depending on the TBSA ( $p = 0.006$ , Fisher's exact test). Again, however, in the delayed referral group, there was no statistically significant difference in the total ketamine dose when taking TBSA into account. ( $p = 0.87$ , Fisher's exact test). The total ketamine dose over the spectrum of TBSA is demonstrated for the acute and delayed referral groups in Figs. 4 and 5 respectively.

## 5. Discussion

Pain is virtually synonymous with burn injuries and all children with a burn will experience pain, regardless of the cause, size or depth of the burn [1]. Burn pain is dynamic and needs constant reassessment. Anxiety is a major factor which can escalate the level of pain in child with a burn therefore requires direct management in its own right. Pain and anxiety have a poorly understood symbiotic relationship in children [1,2]. Poorly controlled pain and anxiety also have a physical and physiological impact which may result in delayed healing [1,9]. Pain has a significant impact on the development of long-term sensory

problems and may precipitate debilitating long-term psychological conditions and chronic regional pain syndromes [10]. Patterson et al showed that pain during hospitalisation was a stronger predictor of psychological adjustment following burn injury than size of the burn or length of hospitalisation [11]. Despite this, pain is often inadequately treated and there are numerous factors which contribute to this inadequate pain control. Medical staff are concerned with possible addiction and other secondary effects of opioids and burn pain is frequently under-estimated [12]. There is a misconception that burn injuries “are just painful”. The expectation is often that burn pain simply cannot be controlled [13]. It has also previously been shown that, even with access to existing protocols, there is poor compliance to these protocols [6].

It is well established that chronic pain is far more complex to manage than acute pain and conventional analgesia strategies remain ineffective against chronic pain. Moa et al. describe it as “Managing chronic pain is to fight a “war” not a “battle” [14]. Our study highlights that patients who present with burn wounds referred late require higher doses of ketamine for dressing changes to achieve adequate analgesia when compared to those who were referred or presented early. One explanation for this is having not received adequate analgesia from the outset of the management of their injury. This is in keeping with Patterson et al.’s findings that there is great value in controlling acute pain during hospitalisation of burns patients [11]. Potential deficits in background analgesia may be contributory to the increase analgesia requirements but this was unmeasured in this study.

Previous studies done in our area have shown that only 38% of the doctors in the peripheral hospitals referring to us give ketamine for dressing changes [6]. Of this 38%, only 8% knew the correct dose of ketamine [6]. This is the basis for our assumption that patients managed at the peripheral hospitals for prolonged periods of time are managed with inadequate analgesia. We feel that the inadequate analgesia contributes to the development of wind up pain in these patients and this is the reason that they require so much more analgesia than patients managed with strict analgesia protocols from the time of their injury.

In this study, the mechanism of injury was not entirely equally distributed in the two groups. The mechanism of injury had a statistically significant effect on analgesia requirements in acute burns and this was due to the fact that partial burns, which are more typical with certain mechanisms, are more painful and would therefore require more analgesia. In the delayed group, however, the mechanism no longer had a statistically significant effect on the analgesia requirements. This is due to the fact that all partial burns had healed by the 21 day cut off for an acute referral and all delayed referrals were deeper burns, regardless of their mechanism. We, therefore, do not feel that the discrepancy in mechanism of injury between the groups played any role in the increased analgesia requirements demonstrated by the delayed referral group.

In both the acute and delayed referral groups, electrical injuries required more than double the total ketamine dose (in mg/kg/days admitted/TBSA). This finding was not surprising as it is well established that disproportionate pain is common after electrical burn injuries [15,16]. Pain following electrical injuries is difficult to manage and, regardless of analgesia modality used, pain is often not satisfactorily relieved [17]. This is likely due to the direct

nerve injury, scar tissue formation around nerves, and neuropathy from post-injury tissue edema that occurs as a result of the heat generated by the electrical current [18,19].

The TBSA in the acute group was larger than the delayed referral group. This is because patients with large burns are usually referred early. Doctors in the peripheral hospitals are more likely to manage smaller burns themselves at district level hospitals and only refer when the wounds are not healing. The patient admitted as a late referral with 40% TBSA, was a patient being managed at another regional hospital without specialist burn surgeons and 23 days after admission the patient deteriorated and was transferred the patient to us. Patients with smaller burns being managed in peripheral hospitals with inadequate analgesia can still develop anxiety, wind up and chronic pain syndromes. This could account for the delayed referral group requiring significantly higher doses of ketamine despite the average burn size in that group being much smaller than the TBSA of the acute group.

In the acute referral group, there is a statistically significant difference in the ketamine requirements depending on the TBSA. However, this is not the case in the delayed referral group. The TBSA has no significant influence in the delayed group and as such, TBSA does not account for the increased analgesia requirements of the delayed referral group.

Management of background pain, neuropathic pain and anxiety would also influence needs during the dressing change, but data is more difficult to collect and has not been included in this cohort. It is highly likely that background analgesia is also poorly addressed in the hospitals outside of the PBS for the same reasons as poor protocol compliance. This is further compounded by lack of drugs available in the state sector such as clonidine and gabapentin. Typically, paracetamol, tilidine, non-steroidal anti-inflammatories and morphine would be available.

## 6. Conclusion

Burn-injured patients with a delayed referral require more ketamine to achieve adequate analgesia than patients referred acutely. Inadequate analgesia in the acute phase of the burn may influence this, therefore adequate analgesia right from the time of the injury is imperative.

## Funding

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## Appendix 1: “Pietermaritzburg Burn Service (PBS) Analgesia Protocols”

<b>Background Analgesia and Sedation</b>			
	<b>Drug</b>	<b>Paediatric</b>	<b>Adult</b>
IV access/ICU/ high care	Ketamine	1 mg/kg IVI titrations	1 mg/kg IVI titrations
		Quick onset quick offset	Quick onset quick offset
Ward Dose 1	Ketamine	5 mg/kg/per os	5 mg/kg/per os
	Midazolam	0.25 mg/kg per os	2.5–5 mg per os
		mixed together	Mixed together
		20–30 min to work	20–30 min to work
Ward Dose 2 (for pain score >3)	Ketamine	Half the previous dose ketamine IMI	100 mg ketamine IMI
	NO Midazolam	5–10 min onset	5–10 min onset
Ward Dose 3 (for pain score >3)	Ketamine	Half the previous dose ketamine IMI	100 mg ketamine IMI
	NO Midazolam		
	The final total dose of Ketamine given at the procedure must be written as the script for the following dressing change, do not leave the inadequate dose as the prescription		
Clinic	Ketamine	5 mg/kg IMI	5 mg/kg IMI
	OR		
	Morphine	–	10–15 mg IMI
Emergency Department	Ketamine	5 mg/kg IMI	5 mg/kg IMI
	Morphine	–	0.05 mg/kg IVI
	Fentanyl	–	50–100 mcg IVI
<b>Background Analgesia and Sedation</b>			
	<b>Drug</b>	<b>Paediatric</b>	<b>Adult</b>
	These are oral doses unless otherwise stated		
Mandatory	Paracetamol (syrup = 120 mg/5 ml)	15 mg/kg 6 h	1 g 6 h
Mandatory	Tilidine (1 drop = 2.5 mg)	1 mg/kg 6 h	–
Mandatory	Tramadol	–	50–100 mg 6 h
Add if pain not controlled and for donor site pain	Ibuprofen (100 mg/5 ml)	10 mg/kg 8 h	400 mg 8 h
	Consider contraindications: Curling’s ulcer, acute kidney injury, comorbidities		

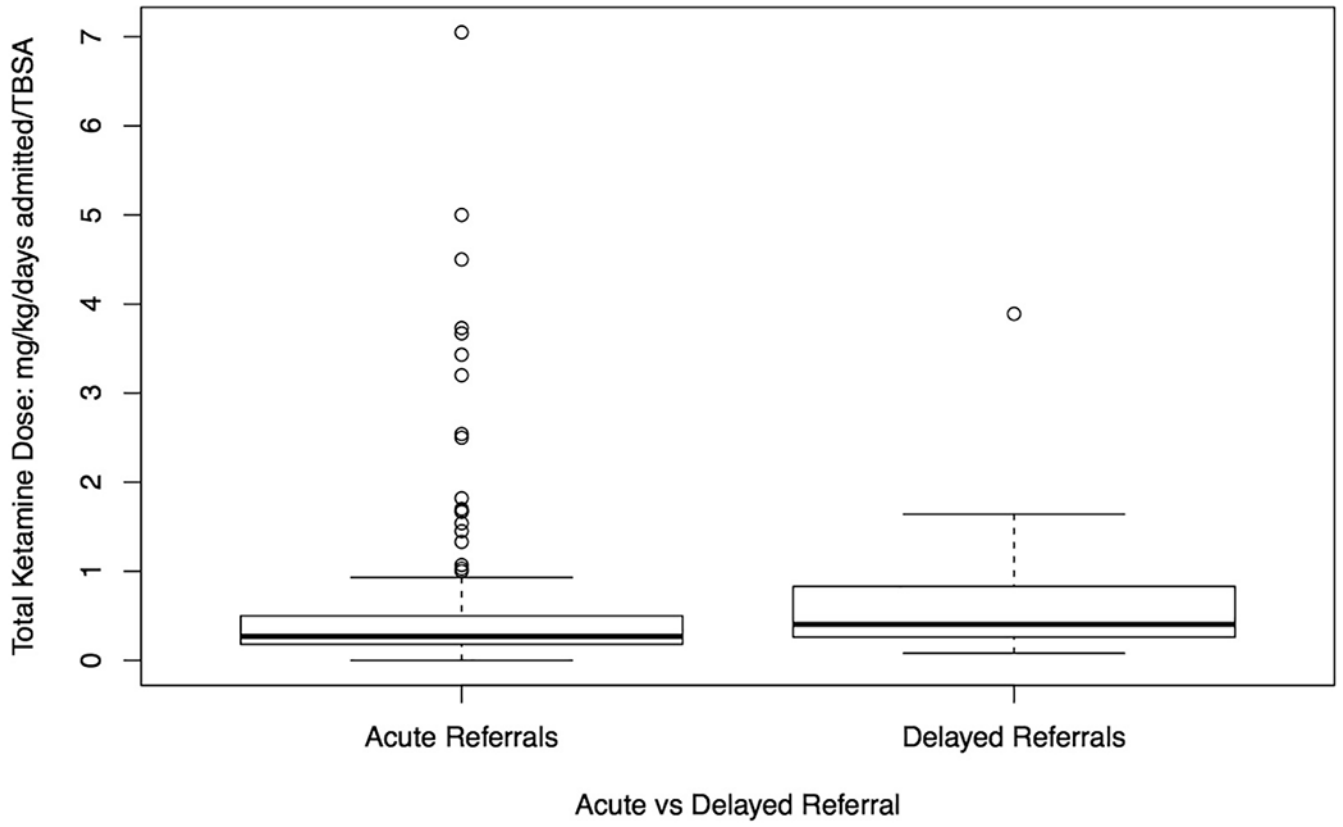
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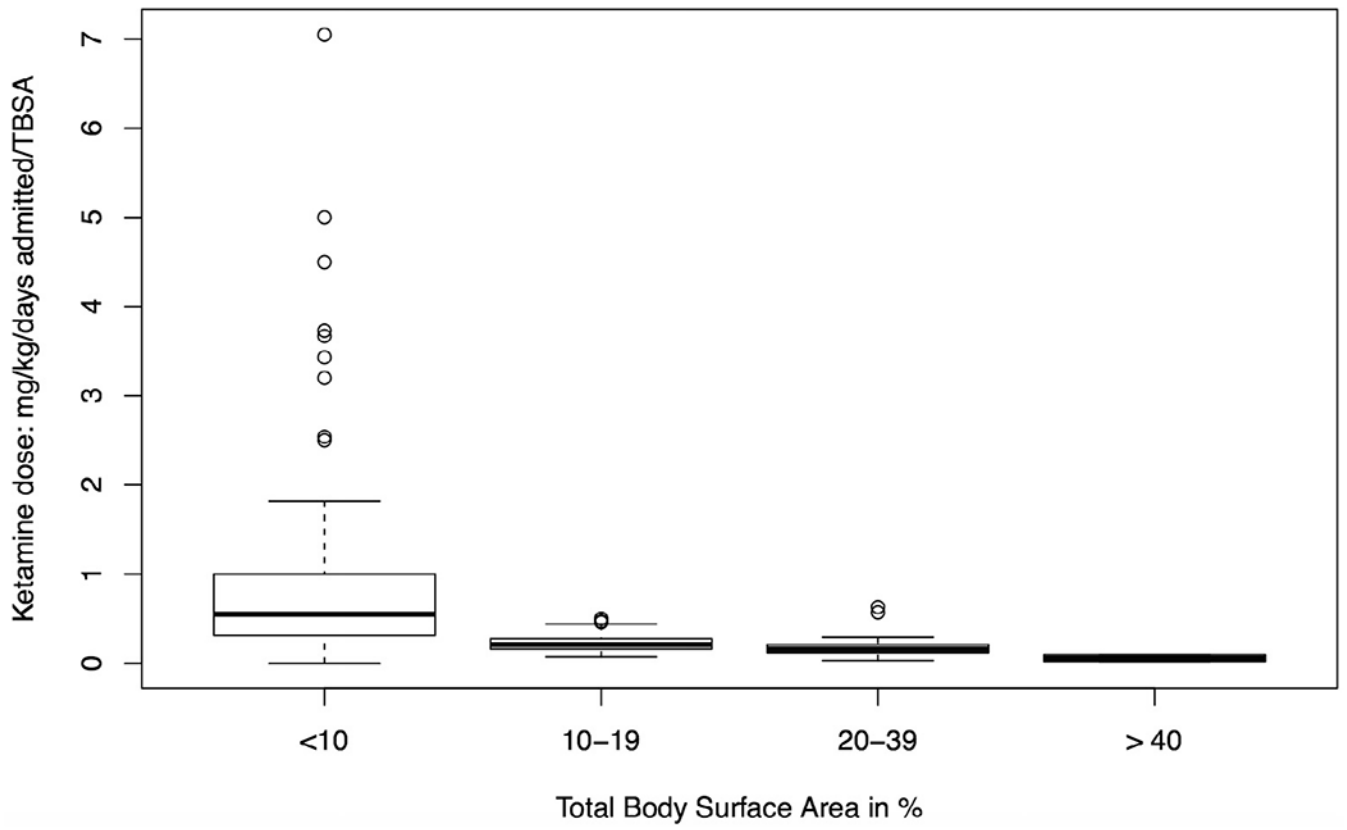


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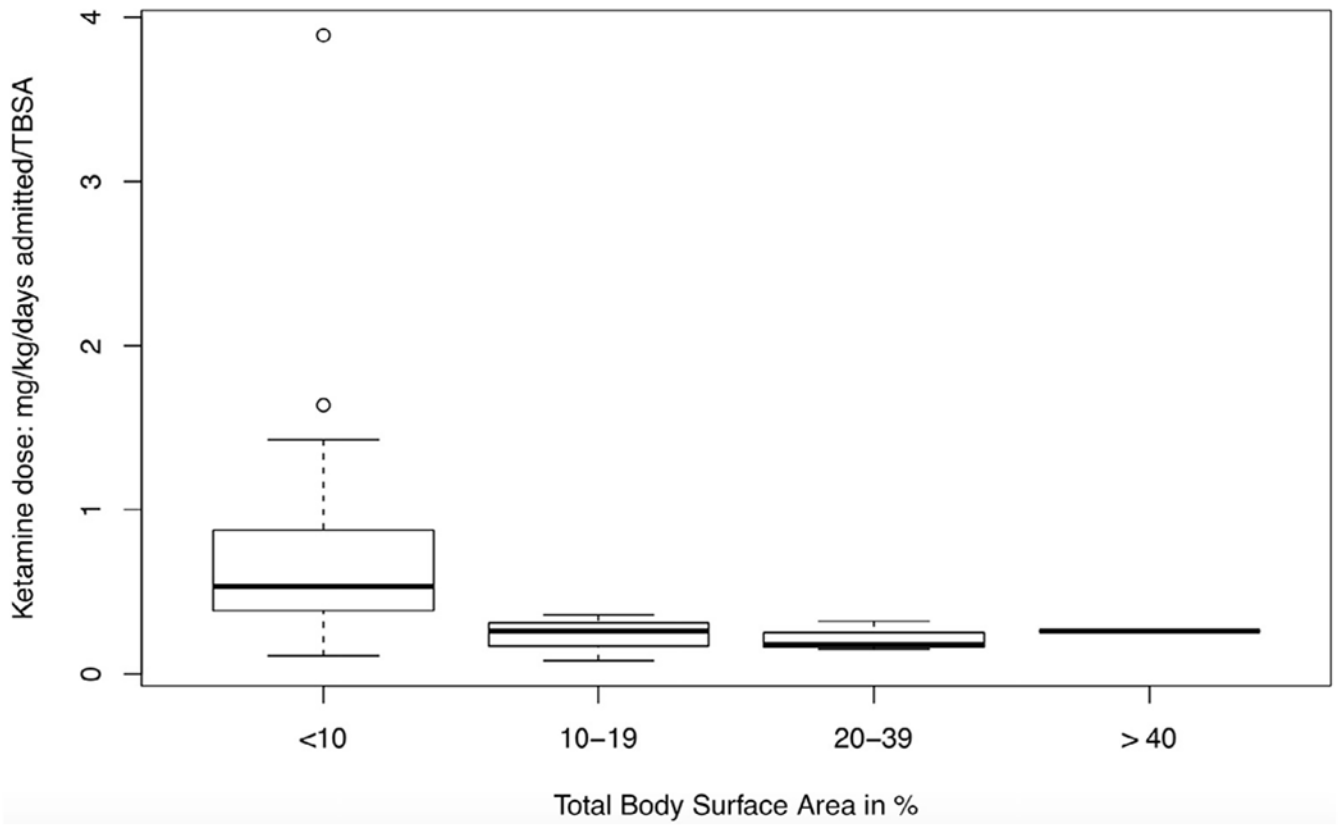




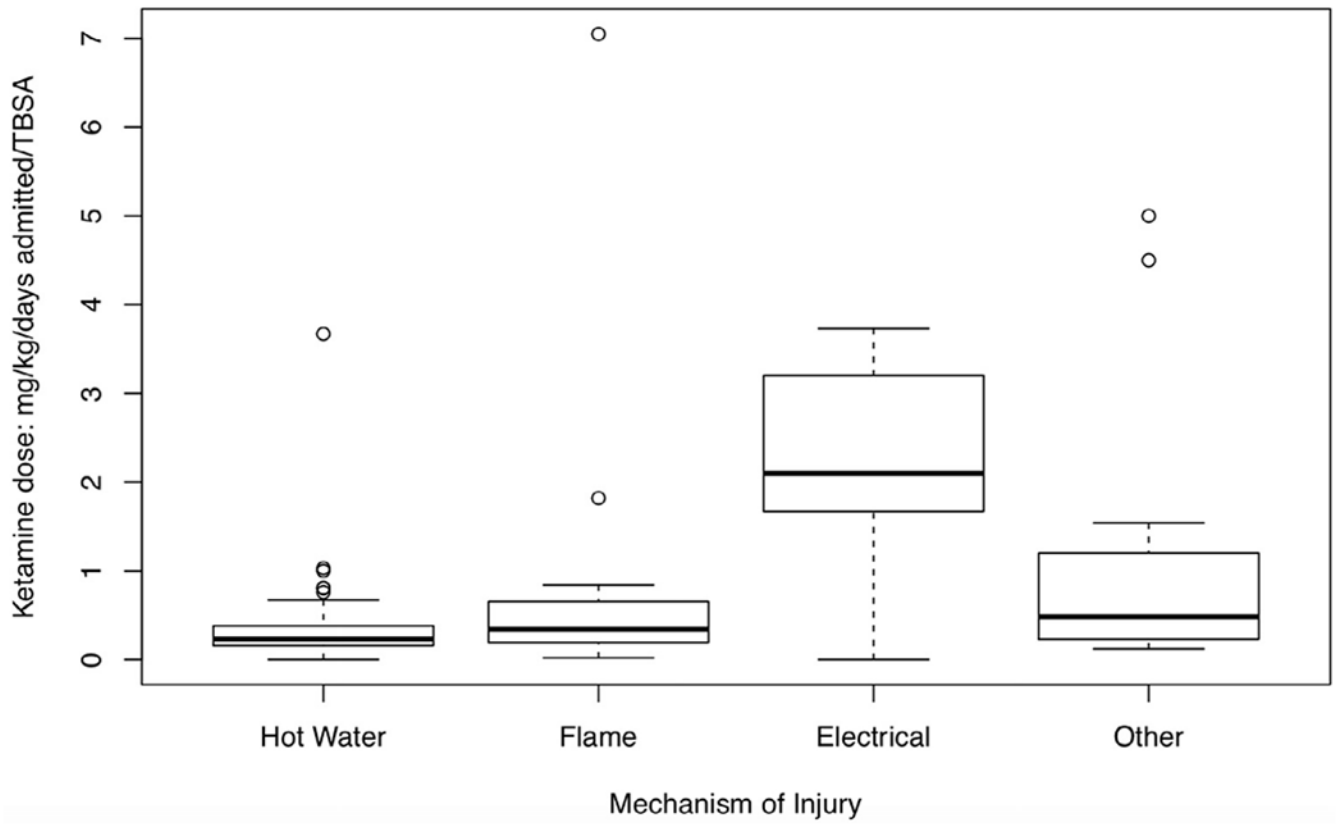
**Fig. 1.** Comparison of total ketamine dose between acute & delayed referrals.



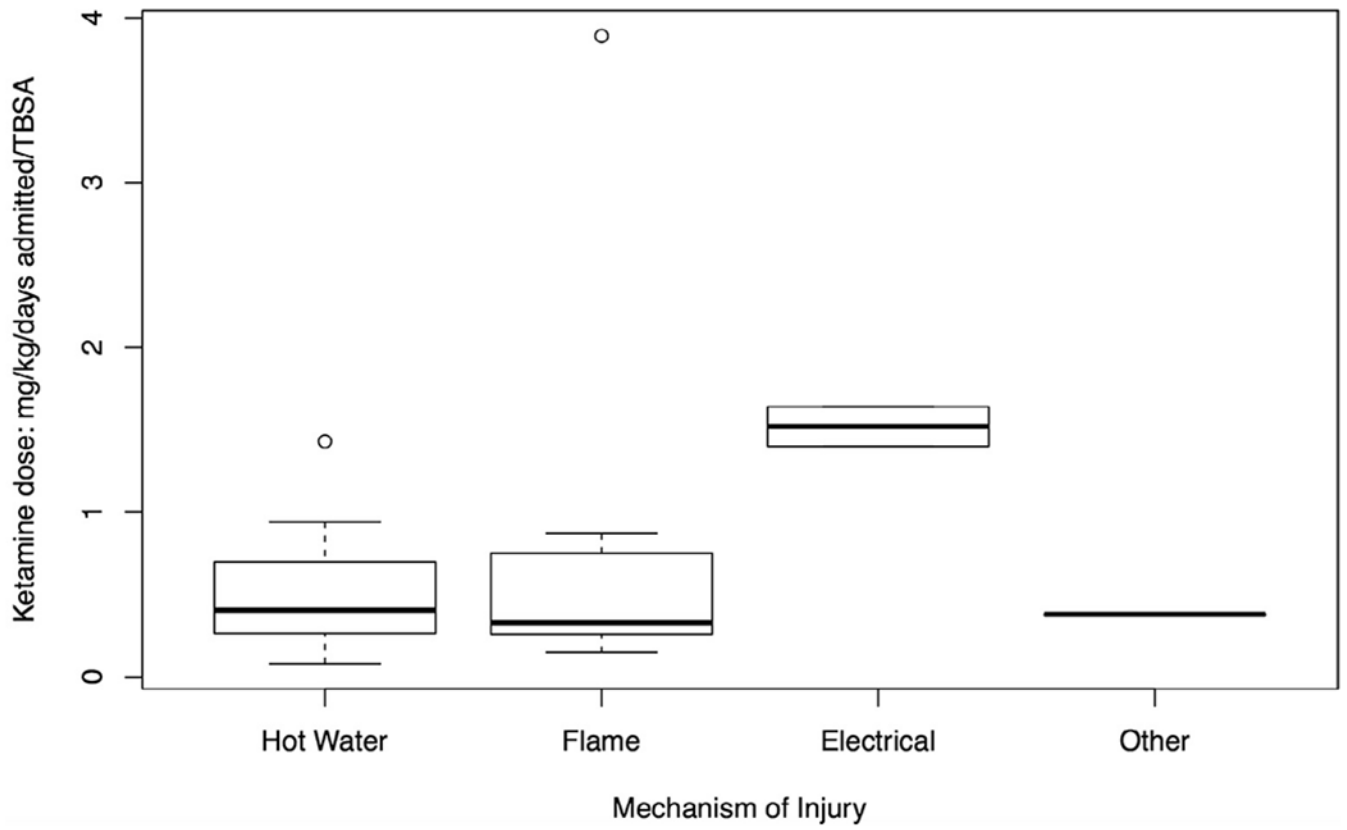
**Fig. 2.**  
Acute group – comparison of total ketamine dose across the TBSA spectrum.



**Fig. 3.**  
Delayed referral group – comparison of total ketamine dose across the TBSA spectrum.



**Fig. 4.** Acute group – comparison of total ketamine dose to mechanism of injury.



**Fig. 5.**  
Delayed referral group – comparison of total ketamine dose to mechanism of injury.

**Table 1**

Comparison between the acute and delayed-referral groups.

	Acute Burn Group	Chronic Burn Group
No in group	167	30
Median Age	2.17 years (Range: 0.17–10.58)	4.80 years (Range: 0.83–10.42)
<i>Gender</i>		
Male	93 (56%)	15 (50%)
Female	74 (44%)	15 (50%)
Median Days Admitted	14 (Range: 1–105)	9 (Range: 5–23)
Median Delay from Burn to Admission (Days)	0 (Range: 0–19)	29.5 (Range: 21–230)
<i>Mechanism of Burn:</i>		
Hot Water Scald	114 (68%)	16 (53%)
Flame	23 (14%)	11 (37%)
Electrical	10 (6%)	2 (7%)
Other	20 (12%)	1 (3%)
Median TBSA	11.0 (Range: 1–50)	4.5 (Range: 1–40)
Median Ketamine Dose (mg/kg/days admitted/TBSA)	0.27 (Range: 0–7.05)	0.41 (Range: 0.1–3.89)