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The addition of ketamine to a morphine nurse or patient controlled analgesia infusion (PCA/NCA) increases analgesic efficacy in children with mucositis pain.

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**The addition of ketamine to a morphine nurse or patient controlled
analgesia infusion (PCA/NCA) increases analgesic efficacy in children with
mucositis pain.**

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Running Title: Morphine/Ketamine infusion for mucositis pain.

Abstract

Aim

To assess the efficacy of adding ketamine to morphine NCA/PCA infusions in treating mucositis pain in children.

Background

Mucositis pain can be very difficult to control in some patients despite the use of parenteral opioids. In our institution we have started adding low dose ketamine to the morphine NCA/PCA in these children in an effort to improve analgesic efficacy.

Methods/Materials

The records of all children receiving a morphine/ketamine PCA or NCA for mucositis pain in our institution from 1999 to 2007 were reviewed. At the time of treatment details of the analgesic management and consumption, pain scores and side-effects were prospectively recorded and then entered on to an electronic database. Ketamine was added at a concentration of 20 or 40mcg/kg/ml with our standard morphine NCA/PCA infusions and protocols being used.

Results

In 28 patients there was no difference between average morphine consumption in the 24 hours pre and post the addition of ketamine (33.1 (\pm 10.7) vs 35.2 (\pm 14.3) mcg/kg/hr, $p=0.45$) but in those with recorded pain scores ($n=16$) the median percentage of pain scores ≥ 4 was 48%(13-100%) pre ketamine versus 33%(0-82%) post ketamine ($p=0.01$). In all patients there was no change in the rates of nausea and vomiting and pruritis pre and post the addition of ketamine and no other significant side effects were reported. No difference was seen between those who had 20 or 40 mcg/kg/ml of ketamine added.

Conclusion

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3 The addition of ketamine to a morphine NCA/PCA improves analgesic efficacy in children with
4 mucositis pain with no increase in the incidence of side-effects.
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9 Keywords: Mucositis, Pain, Morphine, Ketamine, Infusion
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For Peer Review

Introduction

Mucositis is defined as the painful inflammation and ulceration of the mucous membranes lining the digestive tract. It manifests by thinning of the mucosal lining, which may slough off, leading to erythema and ulceration. As the severity increases it is often associated with severe debilitating pain which can prevent talking, eating, swallowing and mouth opening (1,2). Mucositis is usually seen as an adverse effect of chemotherapy and radiotherapy treatment for cancer. The incidence varies with the type and site of cancer and the method of treatment. Of adult patients receiving myeloablative chemotherapy for stem cell transplant 30 to 50 % suffer severe oral mucositis. This increases to over 60% if total body irradiation is part of the regime (1). Children are thought to be at higher risk of developing oral mucositis and incidences from 52-80% have been reported following chemotherapy (3,4).

Mucositis due to chemotherapy typically begins 3 to 5 days after the start of therapy, peaks at 7 to 10 days, and slowly subsides over the next week. The most severe oral ulceration, and severe pain, tends to occur when the patient reaches the nadir of their white blood cell count. The pain can compromise the duration and success of disease management. Severe oral disease and pain makes adequate nutrition difficult and ulceration can predispose to infection with occasionally serious consequences in the immunosuppressed patient. Healing usually occurs within two to three weeks after chemotherapy is ended.

Mucositis pain is often very difficult to control. Meticulous oral hygiene remains the mainstay of treatment but in many cases systemic analgesia is also required. Mild analgesics such as Paracetamol and Non Steroidal Anti-Inflammatory Drugs are often inadequate or contraindicated and the oral and rectal routes of drug administration are usually unavailable. Severe mucositis pain is commonly

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3 treated with potent opioid analgesia given parenterally. The use of patient controlled opioid analgesia
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5 for pain control for children with mucositis has been previously described (5,6).
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9 In our institution morphine nurse or patient controlled analgesia (NCA or PCA), alongside oral
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11 hygiene measures, has been the standard method of treatment for patients with severe mucositis pain.
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13 In a proportion of patients, however, the provision of adequate pain relief has remained problematic.
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15 In an effort to improve analgesic efficacy for this subgroup of patients low dose ketamine is now
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17 added to the morphine PCA or NCA. In this case series we would like to report our experience with
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19 children who received combined morphine-ketamine NCA/PCA for severe mucositis pain looking
20
21 specifically at the effect on analgesic efficacy and the incidence of side effects.
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23

24 **Materials and Methods**

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26
27 The records of all children receiving a morphine/ketamine PCA or NCA for mucositis pain in our
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29 institution from 1999 to 2007 were retrospectively reviewed. At the time of treatment details of the
30
31 analgesic management and consumption, pain scores and side-effects, including nausea and vomiting,
32
33 pruritis, over sedation and hallucinations, were prospectively recorded and then entered on to an
34
35 electronic database. All the children studied were given a demand-led morphine PCA or NCA
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37 infusion at a standard concentration of 20mcg/kg/ml. The decision to add ketamine was made on
38
39 clinical grounds by a Pain Consultant if pain or the disease process were particularly severe, if
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41 adequate pain control was not achieved within normal NCA/PCA protocol limits or adequate pain
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43 relief was proving difficult to achieve and further disease progression was anticipated. Ketamine was
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45 added at a concentration of 20 or 40mcg/kg/ml with standard NCA/PCA protocols once again being
46
47 used (Table 1). Whether 20 or 40mcg/kg/ml of ketamine was added was decided by the Pain
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49 Consultant at the time of the consultation using their judgement of the clinical situation, likely disease
50
51 progression and potential analgesic requirement. Pain was assessed using self-report or behavioural
52
53 observation using validated measures as appropriate (Faces Pain Scale - Revised or FLACC) (7,8).
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55 The PCA or NCA infusions were weaned as clinically indicated as the mucositis improved and were
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57 discontinued once pain could be managed effectively using oral analgesia.
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3 All relevant data was extracted from the electronic database and stored on an Excel spreadsheet.
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5 Statistical analysis was performed using t-tests and paired wilcoxon rank test for non parametric
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7 paired data using SPSS version 14. Differences were considered statistically significant if the p value
8
9 was <0.05.
10

11 12 13 Results

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15 A total of 35 patients with painful mucositis had ketamine added to their PCA/NCA regimen during
16
17 the time period 1999 to 2007. Two could not be studied due to incomplete data collection. This left
18
19 33 patients available for study, 27 of whom had a NCA infusion and 6 a PCA infusion. Five children
20
21 had the ketamine added at the commencement of the infusion. The patient characteristics are shown in
22
23 Table 2. The primary diagnoses are shown in Table 3. Ketamine was added to all the infusions by day
24
25 6 of the infusion with the median being on day 4.
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29 In 28 patients morphine consumption could be compared pre and post addition of ketamine. The
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31 results showed there was no statistical difference between average morphine consumption in the 24
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33 hours pre and post the addition of ketamine (33.1 (\pm 10.7) vs 35.2 (\pm 14.3) mcg/kg/hr, p=0.45).
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35
36 Seventeen patients had 20mcg/kg/ml ketamine added in this 24hr period compared with 11 patients
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38 who had 40mcg/kg/ml ketamine added. Comparison of these 2 groups showed no difference in
39
40 morphine consumption between the two doses of ketamine.
41

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43 Pain scores were available for 16 of these patients, as prior to 2002 pain scores were not entered into
44
45 the database. The scores were recorded hourly and a score of 4 or greater was considered to be
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47 significant pain. Table 4 shows a comparison of the percentage of hourly pain scores greater than or
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49 equal to 4 in the 24 hours pre and post the introduction of ketamine. In all 16 patients there was a
50
51 reduction in the percentage of pain scores greater than or equal to 4 after the introduction of ketamine.
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53 The median percentage of scores \geq 4 was 48%(13-100%) pre ketamine versus 33%(0-82%) post
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55 ketamine, p=0.01.
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59 Of these sixteen patients 12 had 20mcg/kg/ml of ketamine added and 4 had 40mcg/kg/ml. In both
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groups there was a reduction in pain scores \geq 4 pre and post the addition of ketamine but there was no

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3 difference in this effect between the 2 groups. Comparing infusion type in these sixteen patients
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5 showed that 12 had a NCA infusion and 4 a PCA infusion. Again both groups showed a reduction in
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7 pain scores ≥ 4 pre and post the addition of ketamine but once more there was no difference in this
8
9 effect between the 2 groups.
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12 In the 28 children who subsequently had ketamine added to the infusion the incidence of nausea and
13
14 vomiting was 48% in the 24 hours preceding the addition of ketamine. This was reduced, though not
15
16 significantly, to 41% after the introduction of ketamine ($p=0.8$). The incidence of pruritis in these 28
17
18 children was also similar pre and post addition of ketamine (38 and 34 % respectively, $p=0.97$). Again
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20 there was no difference in the incidence of these complications between the group who had
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22 20mcg/kg/ml ketamine added and those who had 40mcg/kg/ml or between those who had a PCA or
23
24 NCA infusion. The overall incidence of nausea and vomiting and pruritis in all 33 patients was 58%
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26 and 44% respectively
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31 In all the patients there were no reports of respiratory depression, sedation, vivid dreams,
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33 hallucinations, confusion or agitation at any point during their PCA/NCA, that could be attributed to
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35 the infusion, pre or post the addition of ketamine. One patient had the ketamine withdrawn after
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37 becoming acutely confused during a septic episode which required admission to PICU.
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40 41 **Discussion**

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43 The findings from our case series of children with chemotherapy induced mucositis suggest that the
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45 addition of ketamine to the routine morphine NCA or PCA regimen improves the efficacy of
46
47 analgesia without increasing side-effects whilst the overall morphine consumption remains the same.
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51 For each individual patient the course of the mucositis, and thus the severity of the symptoms, can be
52
53 very different. The decision at which point to add ketamine to the infusion is made on clinical grounds
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55 and thus comparison between patients is difficult as the analgesic requirements vary enormously in
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57 terms of amount, time course and disease severity. Thus we decided to look at the time period around
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59 the addition of ketamine, thereby allowing each patient to act as their own control. With the decision
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3 to add ketamine being made on clinical grounds it is highly likely that the disease process and
4
5 symptoms were deteriorating at that time with pain control becoming more problematic.
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9 Looking at our data in this way showed that the average morphine consumption in the 24 hours pre
10
11 and post the addition of ketamine did not change but the quality of the analgesia improved, as
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13 assessed by the patients` pain scores. The pain from mucositis is not always constant and can show
14
15 troughs and peaks in severity throughout the day. Both the FLACC and Faces Pain Scale - Revised
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17 pain scores are 10 points scores (7,8). It was felt that a score of 4 or more constituted significant pain.
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19 With pain being measured hourly the percentage of scores that were greater than or equal to 4 can be
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21 used as an overall guide to the efficacy of the analgesia within the 24 hour period.
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25 As the pain associated with mucositis is often severe it is a frequent indication for the use of
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27 parenteral opioids (9). Opioid requirements are often high and increase with the severity of the
28
29 disease (5). In children aged between 12 and 18 years a comparison of morphine given by either PCA
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31 or continuous infusion showed similar efficacy but the morphine use and opioid related side-effects
32
33 were lower in the PCA group (10). Further studies have demonstrated the efficacy and safety of PCA
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35 or continuous infusion of opioids in children with mucositis over long periods of time and that, in
36
37 terms of efficacy, the use of morphine and hydromorphone were comparable and superior to that of
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39 sufentanil (5,6). Review of the adult literature for the treatment of mucositis pain with parenteral
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41 opioids also showed no difference in the efficacy of PCA versus continuous infusion but with the
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43 PCA patients demonstrating lower opioid requirements (11).
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47 N-methyl-D-aspartate (NMDA) receptors have a central role in pain transmission. Activation of these
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49 receptors via the release of glutamate from excitatory synapses plays an important part in central
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51 sensitisation and wind-up and the development of hyperalgesia and allodynia. NMDA receptor
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53 activation also decreases neuronal sensitivity to opioid receptor agonists. Ketamine is a non-
54
55 competitive antagonist at NMDA receptors. It prevents the induction of central sensitisation and
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57 wind-up and the development of opioid tolerance. Ketamine also has agonist actions at spinal opioid
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59 receptors and at monoamine receptors in the descending inhibitory pathways.
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3 The addition of low dose ketamine to opioids could theoretically improve analgesic efficacy for a
4 number of reasons. Ketamine demonstrates anti-nociceptive properties in its own right. Using it as a
5 co-analgesic with opioids may lead to improved analgesia in the same way as other regimens for
6 multi-modal (or synergistic) analgesia. The decrease in opioid tolerance could potentially lead to
7 opioid sparing effects and improved efficacy. Ketamine will also abate the induction of opioid related
8 hyperalgesia.
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12 In adults low dose ketamine is increasingly being used as an adjunct to opioids in the peri-operative
13 period. Recent reviews suggest that addition of ketamine to peri-operative parenteral opioids
14 decreases post-operative opioid consumption, improves analgesic efficacy and respiratory outcome
15 with no increase in side-effects. Though when combined in a PCA the results are equivocal and the
16 use of a single shot administration intra-operatively is insufficient to provide long lasting pain relief
17 (12,13). A single dose of ketamine in the postoperative period has also been shown to rapidly and
18 effectively treat severe pain that was incompletely relieved by morphine (14). Low dose ketamine has
19 also been shown to reduce opioid requirements as well have analgesic efficacy in its own right in
20 adult patients with cancer related pain. Though, as the studies show little homogeneity in terms of
21 design the authors state that more investigation is required to assess the potential benefits and side-
22 effects (15). When added together in the same syringe morphine and ketamine have demonstrated
23 both compatibility and stability (16).
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44 Ketamine has been used to treat cancer related pain in children (17). The use of ketamine as an
45 adjunct to opioids has been less well studied in children. Two systematic reviews which include
46 limited paediatric data show that the addition of ketamine to opioids in the perioperative period is safe
47 and efficacious. The role of PCA morphine and ketamine, however, remains unclear (12,18). Also no
48 opioid sparing effect is seen with the use of a single shot administration intra-operatively (19,20). In
49 children with cancer pain a ketamine infusion alongside opioids has been shown to increase analgesic
50 efficacy, decrease opioid use and improve quality of life (21,22). The use of ketamine only NCA and
51 PCA regimens, without any concurrent opioid use, has been reported in children with inflammatory
52 bowel disease and demonstrated both safety and analgesic efficacy (23).
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3 Our results demonstrate an overall incidence of 58% for nausea and vomiting and 42% for pruritis
4 associated with the morphine and ketamine infusion. This compares with rates of 60% and 36% for
5 our patients with chemotherapy induced mucositis treated with a morphine only NCA or PCA (GOSH
6 pain service database- personal communication). In addition, looking at the 24 hours pre and post the
7 addition of ketamine, there was no increase in the incidence of side effects. In fact the rate of nausea
8 and vomiting fell slightly (48 vs 41%) as did the incidence of pruritis (38 vs 34%). Reviews of adult
9 literature have shown no increase in side-effects, including central nervous system effects, associated
10 with the addition of low dose ketamine to opioids with some studies showing a decrease in the
11 incidence of nausea and vomiting and pruritis (12,24).
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16 The incidence of side-effects in children receiving ketamine and opioids has not been well studied.
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18 Intraoperative use of ketamine demonstrated no increase in psychomimetic effects or nausea and
19 vomiting compared with control groups (19,25,26). In one study where ketamine was also given as a
20 postoperative infusion, 4 out of 25 of the children in the ketamine infusion group had the infusion
21 stopped due to lightheadedness or hallucinations (25). Though the infusion rate was 240mcg/kg/hr
22 compared with our rates of 20 or 40 mcg/kg/hr. The symptoms resolved in all cases within 60 minutes
23 of the infusion stopping. In children with a ketamine infusion for cancer pain there were no adverse
24 effects reported (21,22).
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28 Our results showed that there was no difference between adding 20 or 40mcg/kg/ml of ketamine to the
29 morphine infusion in terms of morphine consumption, efficacy or complications. This was also shown
30 to be the case when comparing infusion technique. The numbers, however, in each of these groups
31 were small, especially in the 40mcg/kg/ml and PCA groups. Thus it is hard to comment on the clinical
32 benefit of using the higher dose of ketamine or a particular infusion technique, especially at the outset
33 of treatment with ketamine. This is an area that requires further study.
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37 Pain associated with mucositis in children can be debilitating and very difficult to treat. Our case
38 series of children with worsening mucositis shows that adding ketamine to morphine improves
39 analgesic efficacy and could potentially be considered a beneficial development in the management of
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3 these children. The decision to add ketamine must also be balanced against the possible adverse
4 effects. Our data shows no increase in the incidence of side effects although due to the limited number
5 of cases and the non-randomised nature of the study further research in this area is required.
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9 10 Acknowledgements

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13 The authors would like to thank Theresa Snelling and Justin Buys for their help in the management of
14 the Pain Control Service Database.
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Legends

Table 1. NCA/PCA Infusion Protocols. GOSH Pain Control Service.

Table 2. Patient Characteristics. Data are mean (range), median or number.

Table 3. Primary diagnosis of patients

Table 4. Percentage of hourly pain scores ≥ 4 for the twenty four hours before and after the addition of ketamine to the morphine NCA/PCA, infusion type and dose of ketamine in the 16 patients studied. Comparison of the median percentages shows a significant decrease in hourly pain scores post the addition of ketamine (48% vs 33%, $p=0.01$).

Table 1.

Up to 50kg = morphine 1mg/kg (+/- ketamine 1mg/kg or 2mg/kg) in 50mls 5% glucose

	Background (ml/hr)	Bolus (ml)	Lockout (mins)
PCA	0 or 0.2	0.5 or 1	5 or 10
NCA	0,0.2,0.5 or 1	0.5 or 1	20 or 30

>50kg = morphine 50mg (+/- ketamine 50mg or 100mg) in 50mls 5% glucose

	Background (ml/hr)	Bolus (ml)	Lockout (mins)
PCA	0	1 or 2	5 or 10
NCA	0, 0.2, 0.5 or 1	1	20 or 30

Table 2.

Sex (male/female)	20/13
Age (yr)	5.1 (0.3–13.6)
Weight (kg)	21.3 (8 – 104)
Infusion Duration (days)	16.8 (5 – 32)
Ketamine Added (day)	4 (0 – 6)

Table 3.

Primary diagnosis	No. of Patients
Acute Lymphoblastic Leukaemia	8
Acute Myeloid Leukaemia	5
Haemophagocytic Lymphohistiocytosis	5
Severe Combined Immunodeficiency	3
Neuroblastoma	4
Lymphoma	4
Kostmanns Syndrome	1
Behcets disease	1
Osteopetrosis	1
Primitive Neuroectodermal Tumour	1

Table 4

Patient Number	Pain scores \geq 4		Infusion Technique (BDG = Background)	Ketamine Dose (mcg/kg/ml)
	pre ketamine(%)	post ketamine(%)		
1	57	40	NCA + BGD	40
2	50	33	NCA + BGD	20
3	30	0	NCA + BGD	20
4	40	33	NCA + BGD	40
5	12	9	NCA + BGD	20
6	11	0	PCA	20
7	60	0	PCA	20
8	100	82	NCA + BGD	40
9	45	37	NCA + BGD	40
10	67	33	NCA + BGD	20
11	44	35	NCA + BGD	40
12	57	33	PCA	40
13	29	0	PCA = BGD	40
14	14	13	NCA + BGD	20
15	91	40	NCA + BGD	20
16	52	41	NCA + BGD	20
	Median 48	Median 33		
	Range 13-100	Range 0-82		

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