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Pain management in 100 episodes of severe mucositis in children

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Figure 1.pptx	

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4 **Pain management in 100 episodes of severe mucositis in children**
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33 **Running Title:** Pain management in mucositis
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37 **Footnote:** *This was presented in part as poster at the Association of Paediatric Anaesthetists, Annual*
38 *Scientific Meeting. London, May 2008.*
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ABSTRACT

Objective: We aimed to review the pain management in 100 episodes of severe mucositis in children and determine the incidence of associated side effects.

Background: Mucositis is a painful, debilitating condition affecting the alimentary mucosa and occurs following many anticancer treatments. Severe pain associated with mucositis may necessitate reductions, delays or termination of anticancer therapy and so intravenous morphine, preferably by patient controlled analgesia (PCA) is the treatment of choice.

Methods: Retrospective review of consecutive episodes of mucositis in children requiring intravenous opioid analgesia over a three year period (May 2006 – April 2009).

Results: In 24/92 (26%) of cases, morphine PCA provided insufficient pain relief and children required adjuvant ketamine therapy. These children had rapidly increasing morphine requirements approaching 1000 mcg/kg/day by day 2 (more than double compared with children on morphine alone), were more likely to be female and tended to be older (median [IQR] age 12 [6 – 12] years versus 7 [3 – 14] years). The addition of ketamine to the morphine PCA appears to be associated with reduced morphine consumption, improved pain scores, causing minimal side effects and no hallucinations.

Conclusions: Children with severe mucositis who have escalating morphine requirements may benefit from the addition of ketamine to their morphine PCA.

Key words: pain, analgesia, ketamine, hematology, oncology, opioid

INTRODUCTION

Oral and gastrointestinal (GI) mucositis is a common, debilitating inflammatory condition affecting the mucosal tissues of the alimentary tract following many anticancer treatments. From a patients perspective, mucositis is one of the most debilitating side effects of their treatment [1] . It occurs in up to 100% of patients undergoing high dose chemotherapy with haemopoietic stem cell (HSCT) or bone marrow transplantation (BMT); over 50% of patients undergoing head and neck radiotherapy; and can occur in 5 – 15% of patients receiving standard chemotherapy.

The severity of mucositis has been evaluated using a number of different scales. Two of the most commonly used scales are the World Health Organisation (WHO) Oral Toxicity Score [2] and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) for Oral Mucositis [3;3;3]. The NCI-CTC score grades severity from 0 to 4 with severe mucositis defined as Grade 3 or 4. Severe mucositis is associated with significant pain that may necessitate dose reductions, delays or premature termination of therapy causing excess morbidity and mortality. Symptoms last from a few days to several weeks. Basic oral care and systemic analgesics are the mainstay of treatment. Intravenous morphine is recommended as the analgesia of choice for children [4].

It is recognised that in some children with cancer, pain may become ‘morphine – resistant’ and the use of ketamine has proved effective [5-8]. Ketamine is a NMDA receptor antagonist and can be used as both an analgesic and anaesthetic. Traditionally its use in routine acute pain management has been limited by fear of psychomimetic side effects. However, recently it has regained popularity at low doses in many types of acute and chronic pain [9-11].

We have used ketamine as an adjunct to morphine in children with mucositis whose pain is difficult to manage with morphine alone. We conducted a retrospective evaluation of the pain management of 100 episodes of severe mucositis in children and present our findings.

METHODS

The clinical records of children with severe mucositis requiring intravenous opioid analgesia between May 2006 and April 2009 were reviewed. The project was registered with the Audit and Service Evaluation Department. Individual parental (or patient) consent was deemed unnecessary for this retrospective study.

We collected data from 103 consecutive episodes of severe mucositis in 85 children (some patients had more than one episode of mucositis). Severe mucositis was defined as Grade 3 or 4 according to the NCI-CTC scales (3).

A standard data collection form was used and the following data recorded: patient demographics, primary diagnosis, 24 hourly morphine consumption, 24 hourly ketamine consumption, pain scores and side effects. Pain was assessed hourly with an appropriate validated tool, most children used a self-reporting tool, Wong and Baker Faces with a 0-10 numerical rating scale [12] or a visual analogue score, but for children unable to self-report the child's nurse used the FLACC observational tool [13]. Pain was charted as is the standard clinical practice in Bristol Royal Hospital for Children on a categorical scale: 0 = no pain (pain score = 0); 1 = mild pain (pain scores 1 – 3); 2 = moderate pain (pain scores 4 – 7); 3 = severe pain (pain scores 8 – 10). The following side effects were recorded: over sedation (somnolent and difficult to rouse), nausea, vomiting, pruritus, urinary retention and psychomimetic.

Pain management protocols are shown in Table 1. Morphine and ketamine are known to be stable when mixed in a saline solution [14]. Patient controlled analgesia (PCA) or nurse controlled analgesia (NCA) was used as appropriate for each child. After initial dosing, the amount of opioid was rapidly titrated to effect under the direction of the 24 hour Acute Pain Service. Ketamine therapy was initiated at the

discretion of the pain service or at the request of the child. In circumstances where a child had previously received ketamine adjuvant analgesia with good effect, it is our routine practice to allow these children to choose their preferred analgesia (morphine or morphine and ketamine PCA / NCA) on subsequent occasions. All children received regular intravenous paracetamol as per the standard practice in our hospital.

Table 1 Pain Management Protocols

Morphine PCA

Morphine 1 mg.kg⁻¹ made up to 50 mL with 0.9% saline

Bolus dose: 1-2mL (=20-40mcg.kg⁻¹)

Background infusion: 0-2mL.h⁻¹ (=0-40mcg.kg.h⁻¹)

Lockout period: 5 min

Initial 4 hour maximum dose*: 400mcg.kg⁻¹

Morphine and Ketamine PCA

Morphine 1 mg.kg⁻¹ + Ketamine 1mg.kg⁻¹ made up to 50 mL with 0.9% saline

Bolus dose: 1-2 mL(=20-40mcg.kg⁻¹ morphine and ketamine)

Background infusion: 0-2mL.h⁻¹ (=0-40mcg.kg.h⁻¹ morphine and ketamine)

lockout period 5 min,

Initial 4 hour maximum dose*: 1000mcg.kg⁻¹

Morphine NCA

Morphine 1 mg.kg⁻¹ made up to 50 mL with 0.9% saline

Bolus dose: 1-2mL (=20-40mcg.kg⁻¹)

Background infusion: 0-2mL.h⁻¹ (=0-40mcg.kg.h⁻¹)

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2 Lockout period: 20 min
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4 Initial 4 hour maximum dose*: 400mcg.kg⁻¹
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9 Morphine and Ketamine NCA
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11 Morphine 1 mg.kg⁻¹ + Ketamine 1mg.kg⁻¹ made up to 50 mL with 0.9% saline
12

13 Bolus dose: 1-2 mL(=20-40mcg.kg⁻¹ morphine and ketamine)
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16 Background infusion: 0-2mL.h⁻¹ (=0-40mcg.kg.h⁻¹ morphine and ketamine)
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19 Lockout period: 20 min,
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21 Initial 4 hour maximum dose*: 1000mcg.kg⁻¹
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26 *The initial 4 hour maximum dose was changed as the child's analgesic requirements changed
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30 RESULTS

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33 Of the 103 consecutive mucositis episodes in 85 children we excluded 3 mucositis episodes. Two were
34 excluded because the child's analgesia was changed from morphine to fentanyl. In one child this was
35 because of significant renal impairment secondary to the chemotherapy; and the other child was changed
36 to fentanyl because of sepsis induced hypotension and fentanyl was considered to provide greater
37 cardiovascular stability in this situation. The third child was excluded because the records were
38 incomplete. This left a total of 100 episodes of mucositis in 82 children for analysis. Of the 82 children,
39 10 had more than one patient episode of mucositis (six children each had 2 episodes of mucositis during
40 the study period; one child had 3 episodes; two children each had 4 episodes; and one child had 5
41 episodes). Patient demographics and diagnosis are shown in Table 2.
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56 68 mucositis episodes (59 children) were treated with morphine only (Group 1); 24 mucositis episodes
57 (19 children) required the addition of ketamine to supplement the morphine analgesia (Group 2); and 8
58 patient episodes (in 4 children) requested ketamine and morphine from the outset (Group 3). These
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children were aged 12 – 14 years (Table 2) and all chose to have ketamine and morphine from the onset of their symptoms because they had found it beneficial and preferable to morphine only on a previous admission. The addition of ketamine, for inadequate pain control or morphine related side effects, was needed in 24 / 92 (26%) of mucositis episodes. Analgesia was administered by PCA in 77 episodes and by NCA in 23 episodes (numbers of PCA and NCA per group: Group 1 = 53 : 15; Group 2 = 18 : 6; Group 3 = 6 : 2 respectively).

The median daily morphine usage for Group 1 and Group 2 are shown in Figure 1. The morphine consumption of children in Group 2 (i.e. those requiring the addition of ketamine to supplement morphine analgesia) was more than double the consumption of children in Group 1 (i.e. those whose pain management required morphine alone). Children in Group 2 were also more likely to be female and older in age (median age 12 years versus 7 years) as shown in Table 2.

Table 2 Patient demographics and diagnosis

	Morphine only	Morphine with ketamine added after initiation of treatment	Morphine with ketamine from initiation of treatment
Number of mucositis episodes (number of children)	68 (59)	24 (19)	8 (4)
Age (years) median [IQR]	7 [3 – 14]	12 [6 – 12]	13 [12 – 14]
Sex M : F (number of mucositis)	43 : 25	8 : 16	4 : 4

episodes)			
Diagnosis: (number of mucositis episodes)			
HSCT	27	9	1
ALL	14	2	
AML	4	4	
NHL	1	2	3
Osteosarcoma	3	1	3
Rhabdomyosarcoma	1	3	1
PNET	8	2	
Other	10	1	

Key: hematopoietic stem cell transplant (HSCT); acute lymphoblastic leukaemia (ALL); acute myeloid leukaemia (AML); non-Hodgkins lymphoma (NHL); primitive neuroectodermal tumour (PNET)

The average duration of symptoms was 7 days in Group 1 (morphine only), and 12 days in Group 2 (adjuvant ketamine). On average, adjuvant ketamine was started after 5 days which corresponded with a reduction in the average daily morphine consumption as can be seen in Figure 1.

In total, we collected data for 627 days of morphine only therapy and 233 days of morphine and ketamine therapy. The average pain scores and incidences of side effects for the total number of days of morphine (n = 627) and morphine and ketamine (n = 233) therapy are shown in Tables 3 and 4 respectively. No episodes of psychomimetic side effects including hallucinations were reported.

Table 3 Median pain scores (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain)

		Pain Score
Group 1:	Morphine only	1
Group 2a:	Morphine + ketamine (before ketamine was added)	2
Group 2b:	Morphine + ketamine (after ketamine was added)	1
Group 3:	Morphine + ketamine from the outset	1

Table 4 Incidence of side effects per total treatment days. Values given as absolute number per total treatment days (%)

	Morphine only days (n = 627) (Group 1 + Group 2a)	Morphine + Ketamine days (n = 233) (Group 2b + Group 3)
Over sedation	19 / 627 (3.0)	3 / 233 (1.3)
Nausea	23 / 627 (3.7)	3 / 233 (1.3)
Vomiting	25 / 627 (4.0)	9 / 233 (4.0)
Pruritus	59 / 627 (9.5)	13 / 233 (5.7)

Urinary Retention	7 / 627 (1.1)	1 / 233 (0.4)
Psychomimetic	0 / 627 (0)	0 / 233 (0)

DISCUSSION

We have described the analgesic management of 100 episodes of severe mucositis in children. Our data show that (24/92) 26% of episodes of mucositis required the addition of ketamine to the standard morphine PCA/NCA in order to control pain. Prior to the addition of ketamine, this group of children had rapidly escalating opioid requirements needing approximately twice as much morphine as those requiring morphine alone (1000 versus 500 mcg.kg.day⁻¹, see Figure 1). Adjuvant ketamine therapy was started an average of 5 days after the onset of symptoms and was associated with morphine consumption of over 1000 mcg.kg.day⁻¹ (see Figure 1). In 8/100 mucositis episodes, a morphine and ketamine PCA was preferred and requested by 4 children who were undergoing repeat chemotherapy regimes associated with mucositis.

Ketamine has been used in the treatment of adult cancer pain and was the subject of a Cochrane review [15]. However there are very few reported uses in children with cancer. Four case reports describe a total of five children [5-8], who received ketamine during end of life care. Finkel [16], describes the use of ketamine in 11 adolescents with uncontrolled pain; in 8 out of 11 ketamine improved pain control and modulated the need for escalating opioid analgesia. In our case series, 24/92 (26%) of episodes of severe mucositis required adjuvant ketamine because of escalating morphine requirements and suboptimal pain control; and in 8 out of 100 mucositis episodes, a ketamine and morphine PCA was requested by children who had experienced this form of analgesia previously and expressed a preference for it. Our data show adjuvant ketamine treatment appears to be associated with reduced morphine consumption and improved pain scores (see Group 2: Figure 1 and Table 3). Ketamine was used in almost one third (28/100) of mucositis episodes (totalling 233 days of treatment) and was well tolerated with minimal side effects (Table 4). Psychomimetic side effects, such as hallucinations, are reported to occur in up to 10% of

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2 children [17] and traditionally have limited the role of ketamine in acute pain management, but none of
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4 our children experienced hallucinations.

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6 Mucositis is a painful condition affecting the mouth and alimentary tract characterised by painful
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8 erythema and ulceration which, when severe, prevents swallowing thereby necessitating intravenous
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10 hydration and parenteral nutrition. Children even find it impossible to swallow saliva. Intravenous
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12 opioids are the analgesia of choice [4]. However, in our series morphine PCA / NCA provided
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14 suboptimal analgesia in 24 / 92 episodes (26%).
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18 Ketamine is a *N*-methyl-D-aspartate (NMDA) receptor antagonist and can be used as both an analgesic
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20 and an anaesthetic. Painful stimuli activate NMDA receptors and cause spinal cord hyperexcitability.
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22 This leads to complex changes causing central sensitization, wind-up phenomena and severe pain [18].
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24 Laboratory data suggests blockage of the NMDA receptor can prevent central sensitisation thereby
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26 alleviating pain [19;20]. In this study of 100 mucositis episodes, we found that in 24 episodes (19
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28 children) where morphine requirements were high and continuing to escalate, the addition of ketamine
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30 appeared to be beneficial. The quality of analgesia improved, and the morphine requirements reduced.
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32 The reason for the apparent 'morphine resistance' in some children is unclear and may relate to
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34 pharmacogenetic reasons. We found a trend towards greater opioid requirements in older females, a
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36 group known to experience more pain and higher morphine consumption in other settings [21]. An
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38 alternative explanation could be opioid tolerance although no child was receiving prior maintenance
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40 opioids. The apparent 'morphine resistant' pain was not related to neuropathic pain. Some children did
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42 have neuropathic pain, but this was clearly distinguishable from the mucositis pain and was treated with
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44 gabapentin administered nasogastrically to good effect. Different chemotherapeutic regimes may induce
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46 hepatic enzymes and accelerate morphine clearance, thereby necessitating higher opioid requirements.
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48 However, we did not record this data and the heterogenous nature of our population would preclude
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50 analysis. Even in a homogenous population this would be difficult to study given the variety of anticancer
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52 protocols which vary by tumour type and stage of disease, the inter-patient variability of toxic effects on
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54 hepatic metabolism and renal clearance, and the vast numbers of chemotherapy agents with overlapping
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2 toxicity profiles [22]. This study did not aim to evaluate the pharmacokinetics but our results indicate that
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4 further investigation in this area is warranted.
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7 Treatment of mucositis hinges on good oral care and analgesia. A study of the perspectives of children
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9 and their parents found that although children were aware of the significance of oral care, the discomfort
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11 associated with oral care forced some children to neglect this aspect of treatment. Parents also found oral
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13 care a stressful event for them and their children. Furthermore, mucositis presented children with a
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15 difficult dilemma whereby it was too painful to chew and swallow food yet they felt very hungry [23].
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17 Adult patients rate pain from mucositis as one of the most debilitating side effects of their cancer
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19 treatment [1]. Optimal pain management guidelines are therefore critically important. Our data suggests
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21 that children with escalating morphine requirements who appear to benefit from adjuvant ketamine,
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23 tended to be older (median age 12 versus 7 years), were more likely to be female, and had a longer
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25 average duration of symptoms (12 v 7 days).
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33 This study has several limitations, namely it is a retrospective analysis, we did not compare analgesia
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35 regimens, and we did not attempt to determine risk factors for 'opioid resistant' mucositis pain.
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37 Benzodiazepines are known to reduce the incidence of hallucinations [24] but are not routinely prescribed
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39 by our Pain Management Team when using ketamine analgesia. However, in our hospital diazepam is
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41 sometimes prescribed for anxiolysis in children by their oncologists. We did not record benzodiazepine
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43 use, which is another limitation of this study. However, we believe this descriptive evaluation of 100
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45 episodes of mucositis in children (totalling 627 days of morphine only therapy and 233 days of combined
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47 morphine and ketamine therapy) adds evidence to the literature regarding the treatment of mucositis and
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49 the use of ketamine in children with cancer-related pain.
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56 In summary, this study shows that morphine PCA provides inadequate analgesia in 26% of children with
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58 severe mucositis (Grade 3 or 4) despite these children receiving higher than average amounts of morphine
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60 (1000 mcg/kg/day compared with 500 mcg/kg/day, see Figure 1). Addition of ketamine to the morphine

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2 PCA / NCA in these children appears to be associated with reduced morphine consumption, improved
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4 pain scores and causes minimal side effects. Therefore, we suggest that children with severe mucositis
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6 who have escalating morphine requirements (approaching 1000 mcg/kg/day) may benefit from the early
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8 addition of ketamine to their morphine PCA.
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10 11 12 13 **ACKNOWLEDGEMENTS**

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For Peer Review

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7 **Figure 1: Daily morphine usage – Group 1 and 2 (data shown as median and interquartile**
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