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All listed authors comply with the journal's Authorship policy.

Ethics Statement

Ethics for this study was approved by the Peter MacCallum Cancer Centre Expedited Ethics Review Committee (Approval number: 18/59R) and in alignment with the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Sublingual Buprenorphine for Acute Postoperative Cancer Pain – A Retrospective Study

Abstract

Background

Sublingual buprenorphine is an atypical opioid that potentially has a wider safety profile than conventional opioids. However, there is a paucity of literature concerning its role in acute postoperative pain.

Aims

To describe the use of sublingual buprenorphine including efficacy and safety for the management of acute postoperative pain at a comprehensive cancer centre.

Methods

A retrospective study of sublingual buprenorphine analgesia after cancer surgery between 1st June 2015 to 31st October 2016. Outcome measures included pain scores (Verbal Numerical Rating Scale), dosage, oral morphine equivalent daily dose before treatment, adverse events, co-analgesia, duration of treatment and length of stay. Patients were categorised as responders or non-responders based on their response. Ethics approved by the Peter MacCallum Cancer Centre Expedited Ethics Review Committee (Approval number: 18/59R).

Results

66 patients were included with a mean age of 62.8 years and 53% were male. 86.3% (55/66) were categorised as responders to sublingual buprenorphine treatment. Pain scores were significantly lower in

responders compared to non-responders after treatment 4.2 vs 7.3 ($p<0.05$). Sublingual buprenorphine was well tolerated with a low adverse event frequency (10.6%), with nausea/vomiting reported most commonly. All patients were prescribed at least one co-analgesic. The mean duration of treatment was 6.2 days and there was no difference in length of stay between groups.

Conclusions

After cancer surgery, patients can benefit from sublingual buprenorphine analgesia due to its safe adverse event profile and overall self-reported efficacy. Further research is recommended to account for confounders including study in a larger cohort.

Key Words: (Sublingual Buprenorphine); (Opioid); (Pain, Postoperative); (Acute Pain); (Cancer Pain)

Introduction

Pain is common in patients with cancer and often has significant impacts on the patient's quality of life and health outcomes (1). Approximately 30 to 50% of all cancer patients experience moderate to severe pain and greater than 50% experience pain from treatment (1). Acute pain after cancer surgery is especially common with evidence showing that 86% of patients reported postoperative pain and 75% of those described experiencing moderate, severe or extreme pain intensity (2). If poorly managed, acute pain can lead to various negative consequences including risk of developing persistent postoperative pain, increased morbidity, functional impairment, delayed recovery, longer length of stay, prolonged opioid use and greater health care costs (2, 3).

The current management of acute postoperative cancer pain involves a multimodal approach, with opioid analgesics playing a significant role in the management of moderate to severe cancer pain (1). Although opioids are effective there are many known side effects including constipation, nausea, vomiting, drowsiness, dizziness and respiratory depression which is severe in 10-20% of patients (1, 4).

Sublingual buprenorphine is an atypical opioid that is garnering increasing interest as an analgesic which could offer alternative benefits compared to conventional opioids like morphine and oxycodone (3-5). Currently, it is well established for the treatment of opioid dependence and not widely used in cancer pain management (3, 4). Atypical opioids differ from conventional opioids by their mechanism of action which does not exclusively rely on μ-opioid receptor agonism (6). Buprenorphine is categorised as a partial μ-opioid receptor agonist, κ-opioid receptor antagonist and opioid receptor-like 1 (ORL-1) agonist (4, 7). Clinical studies have shown that buprenorphine is an effective analgesic and may have a

wider safety profile than conventional μ-opioid receptor agonists including ceiling effect on respiratory depression, reduced cognitive dysfunction, constipation, tolerance, immunosuppression and withdrawal symptoms (3-5, 7). Despite the use of transdermal and intravenous formulations of buprenorphine being well examined for management of chronic cancer pain and acute non-cancer pain, there is a paucity of literature investigating the sublingual formulation with focus on managing acute postoperative cancer pain (3-5).

There is increasing interest in the use of sublingual buprenorphine for acute postoperative pain management, including at the Peter MacCallum Cancer Centre where this study is based (3). Sublingual buprenorphine 200mcg tablet is used by the Acute Pain Service for parenteral analgesia step down, particularly for those who remain nil by mouth or have an ileus, at risk of opioid induced respiratory depression and constipation, or have comorbidities including obstructive sleep apnoea and substance use disorder (5, 7-10).

This study aims to describe the use of sublingual buprenorphine including efficacy and safety for management of acute postoperative pain at a comprehensive cancer centre. The results will help guide future clinical practice and prospective studies of sublingual buprenorphine for cancer pain management.

Method

Study Design

A retrospective review of surgical inpatients prescribed sublingual buprenorphine by the Acute Pain Service (APS) between 1st June 2015 to 31st October 2016 at Peter MacCallum Cancer Centre, Melbourne VIC Australia. All patients admitted following cancer surgery aged 18 years or older were included. Patients with incomplete data about sublingual buprenorphine dosages and effect on pain or were prescribed but not administered a dose of sublingual buprenorphine were excluded from the analysis.

Data was compared between responders and non-responders to sublingual buprenorphine to identify and evaluate factors that impact its clinical use and efficacy. Patients who had documentation of subjectively reported improvement in their pain from sublingual buprenorphine were defined as responders. All other patients were defined as non-responders.

Data was collected from a combination of APS and hospital records. The APS records are collected daily by a member of the APS team during medical rounds and include pain scores, common opioid

adverse events, total oral morphine equivalence for parenteral analgesia use.

Ethical Approval

Ethics for this study was approved by the Peter MacCallum Cancer Centre Expedited Ethics Review Committee (Approval number: 18/59R)

Outcome Measures

The outcome measures collected included demographic and clinical information; reason for admission, sublingual buprenorphine use, pain scores measured as Verbal Numerical Rating Scale (VNRS) and incidence of adverse events.

VNRS is an 11 point rating scale (0-10) where patients verbally report a number that corresponds to their pain intensity where a higher score indicates a greater pain severity and is widely used for assessing postoperative pain (11). This study compared changes in VNRS before commencing sublingual buprenorphine and 24 hours after. The oral morphine equivalent daily dose (oMEDD) of opioids prescribed before starting sublingual buprenorphine and other concurrent co-analgesia were also investigated.

Any potential adverse events that were attributed to sublingual buprenorphine were recorded as having occurred or not. Specific adverse events of interest included nausea and vomiting, central nervous system (CNS) dysfunction (which included sedation/drowsiness, confusion, hallucinations, delirium), respiratory depression, dizziness, constipation and dry mouth.

Statistical Methods

Data on patient demographics and sublingual buprenorphine outcomes were presented descriptively as means, medians and frequencies. IBM Statistical Package for Social Sciences (SPSS v25) was used to conduct all statistical analyses and graph generation. The independent t-test was used to compare the means between responders and non-responders. The paired samples t-test was used to compare the difference in means before and after sublingual buprenorphine in the responder group. Statistical significance was defined as $p<0.05$.

Results

There was a total of 104 patients prescribed sublingual buprenorphine between 1st June 2015 to 31st

October 2016. There were 38 patients excluded, including 12 that were admitted for medical reasons and 26 that had incomplete data, leaving 66 remaining for analysis. Of remaining patients, 57.6% (38/66) were diagnosed with colorectal cancers and 69.7% (46/66) were admitted following a major surgical procedure including laparotomy. The mean age was 62.8 (range 23-85) and the majority were were male 53.0% (35/66). Overall, 86.3% (55/66) were categorised as responders and 16.7% (11/66) were categorised as non-responders. A summary of the patient characteristics is shown in Table 1.

Mean VNRS pain scores before sublingual buprenorphine treatment were not statistically different between the two groups. After treatment, mean VNRS pain scores were significantly lower in the responder group (4.2 VNRS) compared to the non-responder group (7.3) ($p<0.05$). The responder group had a mean VNRS reduction of 17.6% which was not statistically sigificant. In comparison, the non-responder group had a mean VNRS increase of 9.0% after treatment. These comparisons are shown in Table 2 and Figure 1. Before sublingual buprenorphine treatment, 34.5% (19/55) of responders were opioid naïve compared to 18.2% (2/11) of non-responders. Of the non-opioid naïve patients, responders were prescribed 29.7mg oMEDD less opioids before commencing sublingual buprenorphine and 3.4mg oMEDD more of sublingual buprenorphine during treatment compared to non-responders which were both not statistically significant.

Adverse events were reported by seven patients (10.6%) and included nausea and vomiting, CNS dysfunction and dizziness. Nausea and vomiting was reported by four patients (6.1%). CNS dysfunction was reported by two non-responder patients (18.2%) and dizziness was reported by one responder patient (1.8%). There was no reported respiratory depression, constipation or dry mouth. Mean length of stay and duration of sublingual buprenorphine treatment between the two groups were not statistically significant. A summary of sublingual buprenorphine outcomes is shown in Table 2.

All patients were prescribed at least one other co-analgesic alongside sublingual buprenorphine, most commonly other opioids, paracetamol and anti-neuropathic agents (Table 2). Paracetamol was the most common, prescribed to 78.2% (43/55) of responders and 72.7% % (8/11) of non-responders. A greater proportion of responders were prescribed anti-neuropathic agents 61.8% (34/55) compared to non-responders 54.5% (6/11). Contrastingly, a lower proportion of responders 61.8% (34/55) were prescribed additional opioids compared to non-responders 72.7% (8/11).

Discussion

This study showed that sublingual buprenorphine was well tolerated and effective for acute cancer pain management following predominately major surgical procedures. Out of all patients, 57.6% were diagnosed with colorectal cancers reflecting the high rates of incidence in developed countries including Australia (12). Twice as many patients underwent major procedures including laparotomy (69.7%) compared to minor procedures including laparoscopy (30.3%). These demographics provide insight into the background and complexity of patients requiring pain management at comprehensive cancer centres such as Peter MacCallum Cancer Centre.

Sublingual buprenorphine was shown to be well tolerated in this study. The most common adverse event reported was nausea and vomiting, however at a lower frequency than acute non-cancer pain studies. In this study, 6.1% of patients reported nausea and vomiting compared to 14-59% observed during randomised controlled trials (13-16). Nausea and vomiting are significant symptoms and common in advanced cancer and after surgery (17, 18). Additionally, no reported respiratory depression, constipation and dry mouth strengthens the safety of sublingual buprenorphine. Buprenorphine's ceiling effect on respiratory depression and low incidence of constipation are attributed to its partial μ-opioid receptor agonism and could reduce the risk of critical events (5, 7). CNS dysfunction was only reported by two patients in the non-responder group with a frequency of 18.1%. This could be explained by increased cognitive symptoms and delirium risk associated with anaesthesia, during hospital admission and non-responders experiencing poor pain control (19). However, data collection did not include information about anti-emetics or aperients which could have influenced the incidence of reported adverse events. Nevertheless, this study showed that sublingual buprenorphine's safety profile is beneficial in the postoperative period; in particular, reduced constipation, nausea and vomiting.

Comparing responders and non-responders, there were similar results between age, sex, cancer diagnosis, admission reason, duration of treatment and length of stay. The mean age was similar for both responders (63.0 years) and non-responders (61.5 years) as the incidence of most cancers increase with age (12). There was a greater proportion of responders (86.3%) compared to non-responders (16.7%) which showed that sublingual buprenorphine was overall effective in most patients. However, this was not reflected by the pain scores as mean VNRS reduction before and after sublingual buprenorphine within the responder group was not statistically significant. This discrepancy could be explained by the use of subjectively self-reported pain outcomes. Furthermore, these results could have been influenced by known issues associated with opioids and the complexity of postoperative and cancer pain management (1, 2).

Prolonged opioid use may result in cross-tolerance within the pharmacologic class (20). In this study, a greater proportion of non-responders were prescribed opioids and at a higher dose than responders before commencing buprenorphine. 18.2% of non-responders were opioid naïve compared to 34.5% of responders. Furthermore, non-responders were administered a lower mean dosage of sublingual buprenorphine than responders which may have been sub-therapeutic as tolerance requires increased dosages to achieve the desired analgesia (21). Therefore, opioid tolerance should be an important consideration when assessing a patient's potential benefit from sublingual buprenorphine and determining the required effective dosage. Additionally, phenotype differences in pharmacogenetics can affect opioid pharmacology and the participant's response to buprenorphine (22). Incomplete cross tolerance due to a number of different μ-opioid receptor subtypes and different wild-type variants of gene encoding, may contribute to an innate opioid tolerance and thus different response to buprenorphine amongst individuals (20).

This study shows that sublingual buprenorphine can be considered in the clinical setting for the use in postoperative cancer pain. It has properties for being used as a breakthrough medication such as being a quick acting opioid with an onset of effect at 30-60 minutes and a sublingual route of administration, making it suitable for those without an oral route (5, 9). This is important especially in patients having major abdominal surgery and are at risk of developing an ileus or have developed an ileus and cannot tolerate oral medications (8). Buprenorphine is also an atypical opioid lending itself to potentially less opioid-related side effects which is helpful in the acute postoperative period (5).

There were strengths and limitations to this study. Given the paucity of research about sublingual buprenorphine's role in cancer pain management, this study adds to the literature and the findings can be used to support current clinical practice (4). Other strengths of this study included having comparison groups between responders and non-responders and measuring different domains of sublingual buprenorphine clinical outcomes. The major limitation of this study is it being retrospective. This made the study prone to multiple confounding variables that were unable to be excluded and not all related risk factors were identified (23). This study was unable to fully evaluate the confounding impacts of co-analgesics, other non-analgesic medications and timeframe relationship between parenteral analgesia and sublingual buprenorphine treatment. Issues with dry mouth and taste were not discussed as they were not examined in the acute pain literature. Moreover, self-reported sublingual buprenorphine outcomes and collection of data from past medical records had a potential for recall bias and inaccurate or incomplete records (23). Difficulty with accurately measuring pain is a common problem for pain studies as there are no objective methods to fully quantify an individual's experience with pain due to its

complexity and subjective nature (24). In this study, it was difficult to define and group a variety of different surgeries and cancer diagnoses. Finally, this study was limited by a small sample size and data collection from a single hospital site which only partially reflects the heterogeneity of patients in the wider population (25).

Conclusion

This study showed that cancer patients experiencing acute pain after surgery can benefit from sublingual buprenorphine treatment due to its safe adverse event profile and its overall self-reported efficacy. However, the significance of its reported analgesic effect during the first 24 hours of treatment requires further research. This study will help lay the groundwork for future retrospective and prospective studies in a larger cohort, with more recent data and regarding multiple sites.

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Table 1: Patient Demographics		
Characteristics	**Responder Group (n=55), (%)**	**Non-Responder Group (n=11), (%)**
Age in Years (mean)	**63.0**	**61.5**
Sex		
Female	24 (43.6)	7 (63.6)
Male	31 (56.4)	4 (36.4)
Cancer Diagnosis		
Colorectal[†]	33 (60.0)	5 (45.5)
Soft Tissue Sarcoma	5 (9.1)	2 (18.2)
Upper Gastrointestinal[‡]	6 (10.9)	0
Gynaecological[§]	2 (3.6)	2 (18.2)
Lymphoma	2 (3.6)	1 (9.1)
Skin Cancer and Melanoma	3 (5.5)	0
Genitourinary [¶]	3 (5.5)	0
Breast	1 (1.8)	1 (9.1)
Reason for Postoperative Admission		
Major Procedure / Laparotomy	38 (69.1)	8 (72.7)
Minor Procedure / Laparoscopy	17 (30.9)	3 (27.3)

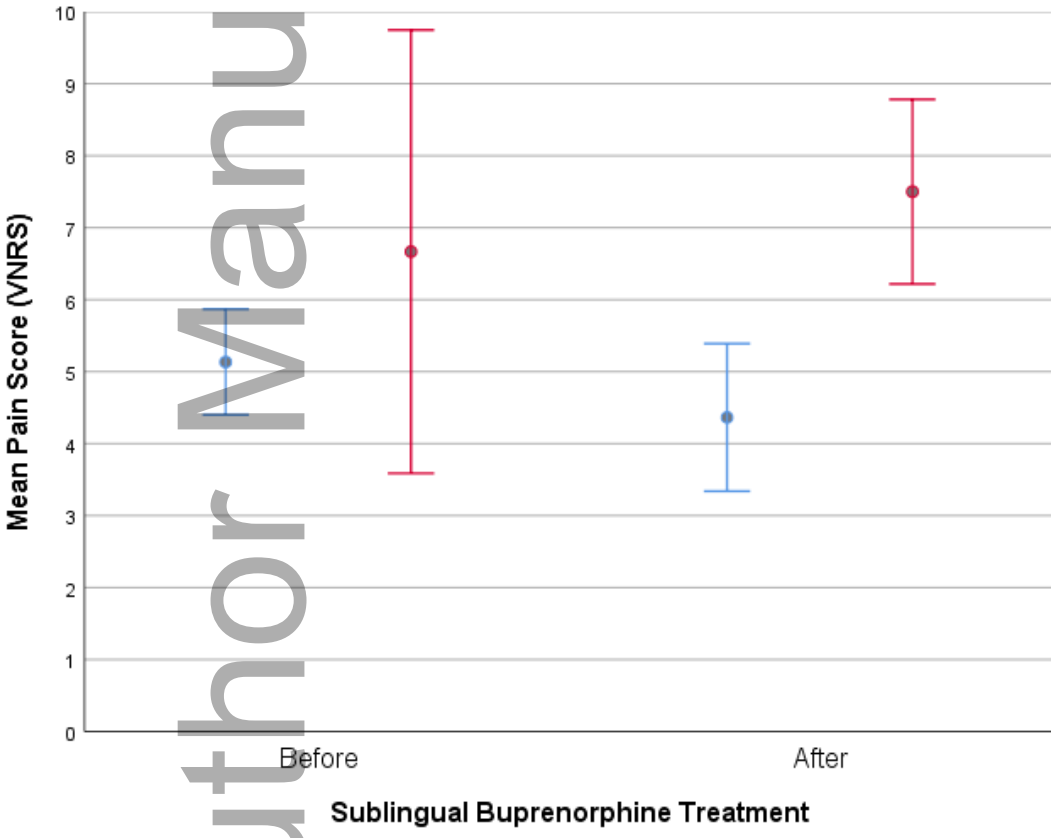
[†]colorectal, anal, appendiceal; [‡]oesophageal, gastric, pancreatic; [§]endometrial, cervical; [¶]renal, bladder, prostate

Table 2: Sublingual Buprenorphine Analgesia Outcomes		
Pain Intensity (VNRS)	**Responder Group (n=55), (%)**	**Non-Responders Group (n=11), (%)**
Before (mean)	**5.1**	**6.7**
After (mean)	**4.2***	**7.3***
Difference in mean (% change)	**- 0.9** (17.6)	**+ 0.6 (9.0)**
oMEDD (mg)		
Total buprenorphine dosage[†] (mean)	**20.1**	**16.7**
Before buprenorphine (mean)	**4.1**	**33.8**
Adverse Events		
Nausea and Vomiting	3 (5.5)	1 (9.1)
CNS Dysfunction	0	2 (18.1)
Dizziness	1 (1.8)	0
Respiratory Depression	0	0
Constipation	0	0
Dry Mouth	0	0
Concurrent Co-analgesia[‡]		
Other Opioids	34 (61.8)	8 (72.7)
Paracetamol	43 (78.2)	8 (72.7)
Neuropathic pain agents[§]	34 (61.8)	6 (54.5)
NSAID	8 (14.5)	2 (18.1)
Epidural (local anaesthetic)	3 (5.5)	0
Duration of Treatment (days)		
(Mean)	**6.2**	**6.2**
1-2	12 (21.8)	4 (36.4)

≥3	43 (78.2)	7 (63.6)
Length of Stay (days)		
(Mean)	**21.8**	**28.7**
1-20	34 (61.8)	6 (54.5)
21-40	14 (25.5)	3 (27.3)
>40	7 (12.7)	2 (18.1)

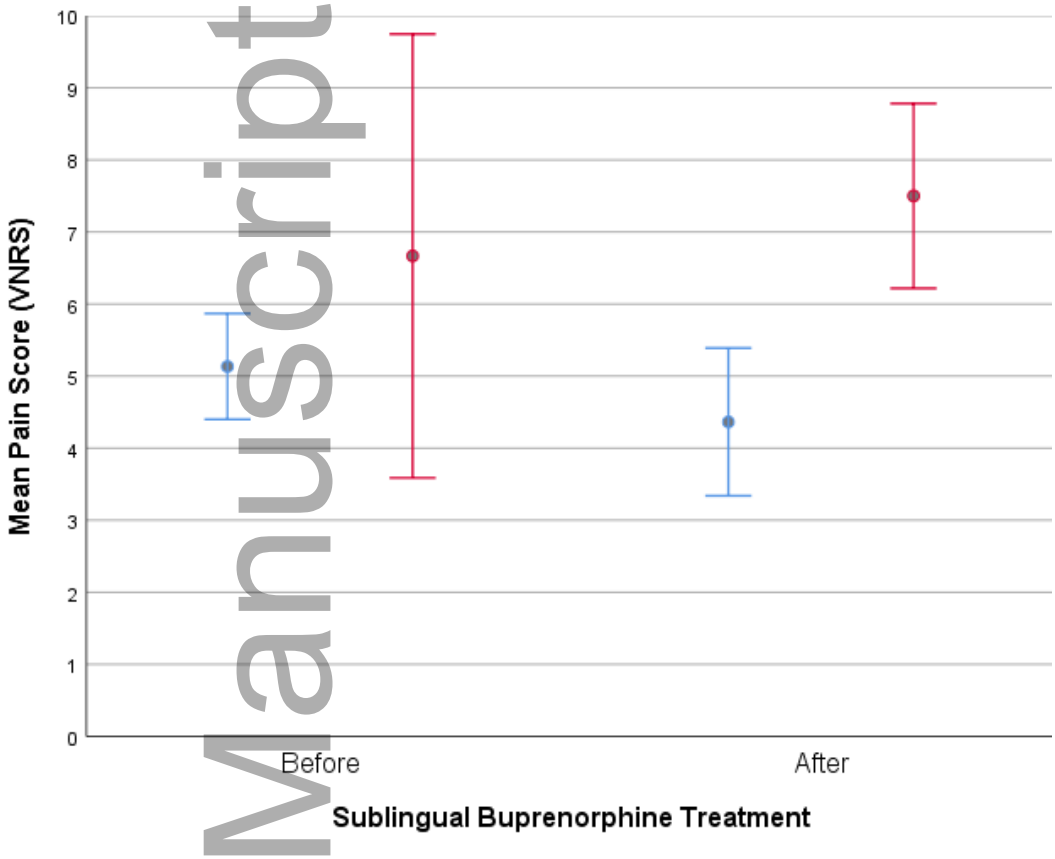
*p value < 0.05; [†]dosage of sublingual buprenorphine administered over 24 hours, [‡]patient prescribed ≥*1 of that category;* [§]pregabalin, gabapentin, amitriptyline, ketamine, clonidine

Figure 1: Mean VNRS pain scores before and after sublingual buprenorphine



Verbal Numerical Rating Scale (VNRS) scores of Responders **(blue)** and Non-Responders **(red)** before and after sublingual buprenorphine. Dots indicate mean VNRS scores. Vertical bars with error bars that indicate 95% confidence interval.

Figure 1: Mean VNRS pain scores before and after sublingual buprenorphine



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