Intermittent Subcutaneous Opioids for the Management of Cancer Pain

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Introduction

PAIN IS A VERY COMMON SYMPTOM in patients with advanced cancer, with a prevalence as high as 80%. The vast majority of patients with cancer pain require opioids for its treatment.^{1,2} Most patients will require alternatives to the oral route for analgesic administration during the course of their disease, due to a variety of factors such as nausea, vomiting, sedation, delirium, bowel obstruction, and swallowing impairment.³ Patients who need parenteral opioids for severe cancer pain usually are managed with intravenous (IV) continuous infusions to maintain stable blood levels due to the short half life of the drugs.⁴ In order to maintain a continuous opioid infusion, patients managed by palliative care and hospice teams in acute care hospitals, inpatient hospices or at home need to use expensive portable or nonportable pumps, with the added costs of maintenance of a central or peripheral intravenous line and the management of rescue analgesic boluses.^{2,4} Intermittent IV opioid delivery results in significant sedation and short duration of effect, due to the short half-life of these drugs.⁴

One alternative is the subcutaneous (SC) route, which offers the possibility of maintaining efficacious pain control with intermittent injections, due to the slower rate of absorption of opioid analgesics.⁵⁻⁷ Intermittent subcutaneous opioid administration with an indwelling subcutaneous butterfly needle is a painless and inexpensive way of achieving pain control in those patients.⁷⁻¹⁰ The Edmonton Injector is a portable, simple, safe, and inexpensive mechanical device for delivering subcutaneous drugs.¹¹

The purpose of this study is to review the results of intermittent SC opioids in a consecutive series of patients with cancer.

Methods

We conducted a retrospective review of 552 admissions (of 514 patients) to the Palliative Care Unit at the Grey Nuns Community Hospital in Edmonton, Alberta, Canada between January 2004 and December 2006. All patients admitted to the Palliative Care Unit are seen by a specialist pal-

liative care physician on a daily basis and undergo opioid dose titration to achieve the best pain control. When parenteral opioids are required, intermittent SC delivery using the Edmonton Injector is the main route of administration.

All patients undergo daily symptom assessment using the Edmonton Symptom Assessment System (ESAS),¹²⁻¹⁴ with assisted completion by a health care provider or family member due to factors such as delirium or fatigue. The daily ESAS pain score was one of the factors considered by the palliative care physician in deciding to maintain or change the intermittent SC route.

We collected from the departmental database and charts of all consecutive patients who needed parenteral opioids information regarding age, gender, diagnosis, details about the use of the device (start date, discontinuation date and reason), and about the injection sites (anatomical localization, duration, and site discontinuation reason).

Intermittent SC route use was considered successful if the patient remained on this route until death or if it was discontinued in favor of an oral or transdermal opioid. A change in modality of treatment to a continuous SC infusion or a change in route of administration to intravenous, intramuscular, or rectal were considered treatment failures. Using a conservative intention-to-treat approach, the use of the intermittent SC route was also considered a failure in all the cases when there was insufficient information available from the charts to determine the outcome.

The Edmonton Injector is a simple and inexpensive portable mechanical device, 7 cm in length and 3 cm in diameter, which is attached to a 50-mL bag containing an opioid solution. With a simple movement, the patient, caregiver, or nursing staff member fills up a 1-mL syringe and with a second movement, the solution is injected into a subcutaneous site through a 25-gauge butterfly needle (Fig. 1). The device has no motor or batteries.^{11,15,16} The opioid solution is prepared according to physicians' orders and usually one 50-mL bag lasts for approximately 50 doses.

We obtained opioid use information for patients who were treated with the Edmonton Injector, including drug name and daily dose. Morphine, hydromorphone, oxycodone, and

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FIG. 1. The Edmonton Injector (adapted with permission from "Your patient has an Edmonton Injector").

codeine were prescribed every 4 hours while methadone was prescribed every 8 hours, unless other problems such as renal failure required different regimes. In addition, rescue opioid injections were available every hour as needed. A total daily opioid dosage was calculated by converting the total opioid dosage during 24 hours to an equivalent dose of parenteral morphine (morphine equivalent daily dose, MEDD), following standard equianalgesic conversion tables.^{17,18}

The cost per milligram of opioids was determined by the hospital pharmacy. For morphine it was CDN\$0.05/1 mg, for hydromorphone it was CDN\$0.11/1 mg, for oxycodone it was CDN\$0.045/1 mg, and for the filtered methadone powder it was CDN\$0.003/1 mg.

To allow for meaningful comparisons considering the differences in potency between the different opioids, the median drug cost was corrected to a median potency-corrected cost relative to morphine. This was done by applying the cited conversion ratios^{17,18} to the median costs and multiplying the total daily dose of each opioid by this potency-corrected amounts (for example, for a patient taking hydromorphone 16 mg/d, the potency-corrected cost would be

$$16\text{mg} \times \text{CDN}\$0.11 \div 5 \text{ (conversion ratio)} = \text{CDN}\$0.352,$$

whereas the uncorrected cost would be

$$16\text{mg} \times \text{CDN}\$0.11 = \text{CDN}\$1.76).$$

Descriptive statistics were used to summarize demographic data and Edmonton Injector related variables. χ^2 tests were used to determine associations between categorical variables. Differences between continuous variables were analyzed using *t* tests for normally distributed data and Wilcoxon rank-sum tests for non-normally distributed data. Significance levels less than 0.05 were considered significant. Analyses were made using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL).

Results

The demographic and clinical characteristics of the study population are summarized in Table 1.

Of 552 admissions (514 unique patients) to the palliative care unit during the study period, 352 admissions (63%) required parenteral opioid administration, and the Edmonton Injector was used in 301 (86%) of those admissions (298 unique patients, with three patients admitted twice during the study period). Success rates are described in Figure 2, and the reasons for discontinuation of the Edmonton Injector are described in Table 2.

The median (interquartile range, IR) duration of the Edmonton Injector use was 11 (5–19) days. The median (IR) number of sites per patient was 1 (1–2), ranging from 1 to 14, and the mean (standard deviation) site duration was 8

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WHO RECEIVED INTERMITTENT SUBCUTANEOUS OPIOIDS

	N (%)
Female gender	159 (53%)
Mean age (range)	61 (19–97)
Diagnosis	
Thoracic	83 (28%)
Gastrointestinal	53 (18%)
Urologic	34 (11%)
Breast	33 (11%)
Gynecologic	28 (9%)
Unknown primary	28 (9%)
Head/neck	9 (3%)
Hematologic	8 (3%)
Noncancer	6 (2%)
Other	16 (5%)

FIG. 2. Opioid administration.

(11) days. Injection sites' anatomical location and frequency of side effects are summarized in Table 3. Site duration, and frequency and type of side effects were not significantly different between different anatomical locations. In all cases, patients who needed rescue IV dosing had refractory pain. Although 20% of the sites developed redness, all patients were able to continue receiving SC opioids using the Edmonton Injector by changing the injection site and changing to IV route was not necessary.

The median number of drugs used with the Edmonton Injector was 1.6, with the majority of the patients using one type of drug. 54 patients used two different drugs during the admission, and 7 patients used three opioids. The overall median MEDD (interquartile range) delivered by the Edmonton Injector was 50 (20–130) mg/d. Types of opioids,

number of patients, total number of days used, average doses, and costs of the drugs used with the Edmonton Injector are summarized in Table 4.

Pain as well as all symptoms showed a trend to decrease after 48h of opioid administration via the SC route. The same trend is demonstrated comparing baseline and 48 hours before discharge or death (Fig. 3).

Discussion

We reviewed the results of intermittent SC opioid administration using the Edmonton Injector among 552 consecutive admissions to a tertiary inpatient palliative care unit (TPCU) in which all patients who need parenteral opioids are first started on SC intermittent opioid injections. Of 352 patients initially eligible for parenteral opioid administration 301 (86%) received the Edmonton Injector.

A previous study of 100 patients showed that this device is safe, simple, and cost-effective, with a low rate of mild side effects.⁸ Since then (for the last 17 years) the TPCU has been performing intermittent SC opioid injections with the Edmonton Injector.

In this 3-year study period, we have found that the majority (88%) of the patients were able to successfully maintain intermittent opioid delivery using the Edmonton Injector. The median duration of the intermittent SC administration was around 11 days, and it has been reported elsewhere that the average stay in the tertiary palliative care unit is around 22 days.¹⁹ This difference probably reflects attempts to control pain using the oral route before the change to parenteral or successful transition to oral/transdermal opioids before discharge.

In the majority (79%) of admissions in which the use of intermittent SC infusions was considered successful, patients died on the Edmonton Injector. In the remaining 21%, route change to oral or transdermal was performed.

TABLE 2. INTERMITTENT SUBCUTANEOUS (ISC) ADMINISTRATION: SUCCESS, FAILURE, AND REASONS FOR DISCONTINUATION

	N (%)
Success	266 (88%)
Reasons for ISC discontinuation	
Death	209 (79%)
Discharge	39 (15%)
Change to oral	17 (6%)
Change to transdermal	1 (<1%)
Failure	35 (12%)
Reasons for ISC discontinuation	
Change to IV	8 (23%)
Side effects	4 (11%)
Insufficient information	23 (66%)
Total	301 (100%)

IV, intravenous

TABLE 3. INJECTION SITES: ANATOMIC LOCATION DISTRIBUTION AND REASONS FOR CHANGE

	N (%)
Site location	
Arm	331 (61%)
Chest	95 (17%)
Thigh	83 (15%)
Abdomen	34 (6%)
Back	2 (<1%)
Total	545 (100%)
Reasons for site change	
Redness	63 (20%)
Bleeding	26 (8%)
Leakage	16 (5%)
Swelling	5 (2%)
Pain	4 (1%)
Inadvertent removal	1 (<1%)
Other/unknown	193 (63%)
Total	308 (100%)

Among the admissions in which the use of intermittent SC infusions was considered a failure (12%), the majority (23/35; 66%) were considered as such because of lack of information from the charts. This is due to the retrospective nature of the study, and we suspect that many of these admissions resulted in successful management with intermittent SC opioids. It was necessary to change route from the SC to the IV in 8 of 301 (3%) admissions, very low as previously described for our setting.⁸ The use of intermittent injections was considered a failure because of side effects in only 4 of 301 (1%) of the admissions.

The 8-day overall duration of the sites was slightly longer than previously reported for intermittent infusions (6.5 days)⁸ and for continuous infusions of opioids (7 days).²⁰ In contrast with our previous data, no site infections were detected and accidental needle pulling was reported in only one case (< 1%).⁸ This suggests that the rate of local side effects seems to have decreased over time as the team's expertise in the use of intermittent SC opioid delivery increased. It is important to notice that our data might not be

representative of the average inpatient hospice or acute palliative care population in the United States, since in most cases the duration of admission is shorter than in Canadian centers.

We found that the morphine equivalent daily doses administered subcutaneously were somewhat lower than the previously described doses administered using the same route in palliative care patients.^{8,11} The most frequently used opioid was hydromorphone. It had already been reported to be well tolerated when used subcutaneously both as continuous and intermittent infusion.^{21–24} Our results confirm those findings for the intermittent SC delivery. Subcutaneous oxycodone and methadone were also used and well tolerated by the patients at our center. Unfortunately, these drugs are not widely available for parenteral administration in other countries.

We have encountered a progressively decreasing number of respondents to the ESAS assessments. As patients progress toward the end of life and delirium becomes more common and their ability to adequately report their symptoms decreases.²⁵ This, as well as the discharge and death of some patients, are the main reasons for the progressive reduction in the number of ESAS respondents, as seen in Figure 3. This reduction impairs our ability to accurately detect symptom changes between the different time points. We observed ESAS pain scores around 4 after one week of admission to the palliative care unit. A previous report in another specialist palliative care unit showed average pain scores of around 4 after 1 week of admission.²⁶ Our findings for the ESAS pain scores at 48 hours before death confirm previous findings in the same palliative care unit.⁸ Whereas it is not possible to draw definitive conclusions about pain evolution in this retrospective study, it showed a trend toward improvement after the use of intermittent SC opioid administration. A recent randomized, double-blinded crossover study showed that there are no differences in analgesic and adverse effects between continuous SC infusion or intermittent SC delivery of opioids in patients with stable cancer pain.²⁷ The ESAS pain scores suggest that patients achieved adequate pain control with intermittent SC opioids, similarly to results obtained by the intravenous route in other acute inpatient settings.

Continuous intravenous opioid infusions involve a variety

TABLE 4. OPIOID ANALGESICS DELIVERED BY INTERMITTENT SUBCUTANEOUS ADMINISTRATION: NUMBER OF PATIENTS, DAYS USED, DAILY DOSE, AND MEDIAN DAILY COST

	Number of patients ^a	Median (interquartile range) number of days used	Median (interquartile range) MEDD (mg/day)	Median (interquartile range) daily potency-corrected cost ^b (Canadian dollars)
Hydromorphone	150	6 (3–12)	94 (35–233)	\$2.07 (0.78–5.12)
Morphine	93	7 (3–15)	39 (16–64)	\$1.95 (0.78–3.21)
Oxycodone	66	6 (3–14)	71 (28–208)	\$2.14 (0.84–6.23)
Methadone	9	1 (1–4)	730 (167–840)	\$0.27 (0.06–0.32) ^d
Codeine	1	9	6	\$1.57
Total	319 ^c	9 (4–17)	64 (23–176)	\$2.02 (0.77–4.54)

^aNo information available for 47/298 patients (16%).

^bMedian daily cost per patient, corrected by potency relative to morphine.

^cSome patients used more than one drug.

^d $p < 0.0001$ (comparison with the total median daily cost).

MEDD, morphine equivalent daily dose.

FIG. 3. Median (interquartile range) Edmonton Symptom Assessment System (ESAS) pain scores at four time points.

of very high costs that are not present in the intermittent SC modality presented in this manuscript. A central or peripheral line must be provided, with increased cost.²⁴ Continuous SC infusions of opioids were already proven to be effective^{21,23,28} and are less expensive than the intravenous, but there is still the need for expensive infusion pumps.^{24,29} Including the device cost, pharmacy time, nurse education time, and maintenance, the daily cost for intermittent SC opioid delivery using the Edmonton Injector was calculated as CDN\$1.65.⁸ The set-up time for the Edmonton Injector at the bedside is less than 2 minutes, while patient-controlled analgesia (PCA) pumps require considerable time in programming and documentation in the chart. When using the Edmonton Injector, the process of drug administration and documentation in the bedside form takes less than one minute of nursing time.

Drug costs are also substantially reduced with the use of the Edmonton Injector, since up to a 100 mL of the opioid solution is prepared per bag by using less expensive commercially available powder rather than existing parenteral solutions. Using powder to reconstitute opioid solutions is much less expensive but also associated with potential for higher rates of pharmacy error and increase in pharmacy time and equipment. These issues should be addressed in future research regarding opioid cost and utilization.

Parenteral opioid management with intermittent SC injections is highly effective and has minimal cost. In developing countries, where costs play a major role in reducing opioid availability,³⁰ this administration modality may be especially useful. In addition to the lower cost, patients and families can manage the intermittent administration at home with minimal training, which is not true for the management of IV pumps. Providing patients and families with preloaded syringes with the opioid solution to be intermittently injected into a SC site is a way of providing excellent pain control for

patients at home in whom oral administration is not possible, the Edmonton Injector is not available, and the use of electrical IV pumps is not an option because of its high cost.

Our group is now developing a prospective study to validate the findings of this preliminary retrospective study.

Conclusion

Intermittent SC opioid administration with the Edmonton Injector is a safe, highly effective, and inexpensive way to manage cancer pain. The use of intermittent SC opioids allowed adequate pain control with minimal side effects. It has the potential to decrease health care costs related to the treatment of pain in cancer patients both in the inpatient setting as well as in the community. Intermittent SC opioid injections are especially interesting to help improve care of patients with cancer in areas where financial resources are scarce and opioid availability is limited, such as developing countries. The Edmonton Injector is an extremely inexpensive device which can be used both in inpatient and outpatient settings and easily operated by nurses, families, and patients.

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Author Disclosure Statement

No competing financial interests exist.

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