ORIGINAL ARTICLE

Effectiveness of opioid rotation in the control of cancer pain: The ROTODOL Study

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ABSTRACT

Objective: *To assess the effectiveness of opioid rotation (OR) to manage cancer pain. To describe the adverse events (AEs) associated with OR.*

Setting: *Thirty-nine tertiary hospital services.*

Patients: *Sixty-seven oncological patients with cancer-related pain treated at outpatient clinics.*

Intervention: *Prospective multicenter study. Pain intensity was scored using a Numerical Rating Scale (NRS) of 0-10. Average pain (AP) intensity in the last 24 hours, breakthrough pain (BTP), and the number of episodes of BTP on the days before and 1 week after OR were assessed. The pre-OR and post-OR opioid were recorded. The presence and intensity of any AEs occurring after OR were also recorded.*

Results: *In the 67 patients evaluated, 75 ORs were recorded. In all cases, the main reason for OR was poor pain control. Pain intensity decreased by ≥2 points after OR in 75.4 percent and 57.8 percent of cases for AP and BTP, respectively. If the initial NRS score was ≥4, a decrease below <4 accounted for 50.9 percent and 32.3 percent of cases for AP and BTP, respectively. The number of episodes of BTP also decreased significantly ($p < 0.001$). A total of 107 AEs were reported, most of which were mild in intensity, with gastrointestinal symptoms predominating.*

Conclusions: *Opioid rotation appears to be both safe and effective in the management of basal and breakthrough cancer pain.*

INTRODUCTION

Opioids play an essential role in pain management in patients with advanced cancer.[1] Effective pain control can be achieved in more than 90 percent of cases when the World Health Organization (WHO) method for pain relief[1] is used.[2,3] However, in an important minority of patients, analgesia is insufficient despite high opioid doses, and some patients may experience intolerable adverse effects regardless of analgesic control.[4] Nonresponse to opioid treatment or development of toxicity during opioid use may be due to a number of factors, including type of pain (eg, neuropathic pain), temporal pattern (eg, chronic or breakthrough), development of tolerance, tumor progression, individual patient characteristics, and finally, the specific characteristics of each drug and/or pharmacokinetic differences between opioids (such as formation of active metabolites and route of administration).[5,6]

In recent years, a growing body of evidence has shown that when a strong opioid produces undesired adverse side effects, switching to an equally strong but different opioid can decrease those adverse effects and improve pain control.[7-9] This approach is known as opioid rotation (OR) and is defined as the substitu-

tion of one opioid for another to achieve a balance between effective analgesia and adverse effects.[7,10] The benefits of OR derived from individual variability in analgesic response to opioids, in which various factors such as age, gender, type of cancer, changes in renal or hepatic function, or emotional status can all play a role.[11] Numerous factors, including pharmacodynamic variability, genetic variability,[12,13] neuronal changes in response to chronic opioid exposure,[14-16] the specific *N*-methyl-D-aspartate receptor activity of some opioids,[17,18] and the phenomenon of receptor blockade[19] may be involved in this mechanism. Variability in pharmacodynamic parameters includes differences in bioavailability, pharmacological interactions, different metabolism routes, and different production of active metabolites.[20,21]

Previous studies of OR have focused primarily on assessing toxicity, tolerance, and the management of difficult-to-control pain, or on determining dose equivalence between opioids.[22-26] Apart from Mercadante et al.,[27] none of these studies either suggest how to evaluate the effectiveness of OR for pain control or address the benefits of OR in improving breakthrough pain (BTP).

This knowledge gap, together with the dearth of OR studies performed in Spain, has prompted us to design and conduct the present longitudinal, prospective, multicenter study. The main aim was to assess the effectiveness of OR in the management of cancer pain in Spain. A secondary objective was to describe toxicity produced by OR.

MATERIAL AND METHODS

Thirty-nine different hospital departments (see Appendix for investigators and institutions) in Spain participated in this study. Of these, 14 (36 percent) were medical oncology departments, 16 (41 percent) radiation oncology departments, and 9 (23 percent) were palliative care. The participating departments prospectively collected data on 257 patients undergoing outpatient treatment during the period from April 1, 2004 through March 1, 2005. The study was approved by the Research Ethics Committee of the Hospital Universitari de Bellvitge in L'Hospitalet, Barcelona, Spain.

Opioid rotation: definition

For the purposes of the present study, OR was defined as a switch from one strong opioid to another strong opioid, regardless of the reason(s) for switching. Changes in route of administration or switching from an immediate-release to a sustained-release formulation of the same opioid were not considered OR.

Patient selection and assessment criteria

During the inclusion period, all consecutive patients who attended the outpatient clinics of the participating departments were eligible to take part in the study. Inclusion criteria were as follows: age ≥ 18 years, diagnosis of cancer, current cancer pain, and the need to implement OR due to poor control of cancer pain. All patients provided written, fully informed consent prior to study enrollment. Determination of patient eligibility for OR due to poor pain control was based on clinical criteria.

The following data were also recorded for each patient: age, sex, Karnofsky performance status score, tumor type, pain type, pain classification according to the Edmonton Staging System (ESS),[28] pre-OR opioid, post-OR opioid, opioid route of administration, and the morphine equivalent daily dose (MEDD) of the pre-OR and post-OR opioids. Given the differences between the various published opioid conversion tables, the participating centers all agreed to use a single conversion table.[29] If opioid rotation was initiated due to pain and toxicity, the baseline dose was reduced by 25-50 percent before the change; if no toxicity was present, then an equivalent dose was used for the rotation. Pain intensity was scored using a Numerical Rating Scale (NRS) ranging from 0 to 10, where 0 was "no pain" and 10 was "the worst pain imaginable." Both average pain (AP) intensity over the last 24 hours and BTP (transient increase in pain to greater than moderate intensity occurring on a baseline pain) were assessed on the days prior to OR implementation and at 1 week post-OR. The number of BTP episodes in the 24 hours preceding OR and at 1 week post-OR was also recorded. For the purpose of this study, OR was considered efficacious if it led to a ≥ 2-point decrease in pain score within 1 week of switching.

An evaluation, conducted in person or by telephone by the attending consultant, took place 1 week after the OR. During this week, changes in opioid dosage were allowed and recorded in the questionnaire. Other than this 1 week evaluation, patient appointments were scheduled according to standard care (ie, in terms of their clinical needs)

and not for study-related purposes), and there were no other study-specific appointments or phone calls. Follow-up data were recorded on the study form when patients attended their regular appointments. During these follow-up visits, patients were asked to notify the investigators of any change in their opioid regimen made by other professionals (eg, general practitioners or emergency room physicians).

The emergence of any adverse event (AE) and its intensity was also recorded using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3 scale.[30] Patients were followed for 90 days. This follow-up period was chosen to coincide with the median follow-up time at outpatient palliative care clinics in Spain for patients with very advanced cancer.[31]

Statistical analyses

Data were analyzed using SPSS for Windows v. 12.0 (SPSS Inc., Chicago, IL). Categorical or dichotomous variables were described as absolute and relative frequencies. Continuous variables were described using measures of central tendency (mean or median) and 95% confidence intervals (95% CI). The marginal homogeneity test for unpaired data was used for comparisons of pain intensity at the different time points of evaluation. All tests were two tailed, with a type 1 error rate of 5 percent.

RESULTS

Overall results

A total of 75 ORs were performed in 67 patients. Most patients (60 patients; 89.5 percent) had only 1 OR, while 6 patients (8.9 percent) had two, and 1 patient (1.5 percent) had 3 ORs. The mean patient age was 61 years (range, 27-91), and 73.1 percent (49 patients) were male. Pain was nociceptive in 36 patients (53.7 percent) and mixed or neuropathic in 31 (46.3 percent). Nearly two thirds of patients had poor prognosis (stages II-III) pain (Table 1).

The attending specialist who directed the OR was a radiation oncologist in 29 cases (43.3 percent), a palliative care physician in 25 cases (37.3 percent), and a medical oncologist in the remaining 13 patients (19.4 percent).

In 18 ORs (24 percent), opioid toxicity was cited as a reason (in addition to pain) for switching. The most common AEs before OR were somnolence (12

Table 1. Demographic characteristics of patients requiring opioid rotation (OR)

Characteristic	N	Percent
Number of patients undergoing OR	67	100
Patients with 1 OR	60	89.5
Patients with 2 ORs	6	8.9
Patients with 3 ORs	1	1.5
Clinical service		
Medical oncology	13	19.4
Radiation oncology	29	43.3
Palliative care	25	37.3
Gender		
Females	18	26.9
Males	49	73.1
Age (median and range)	61 years	27-91
Karnofsky index (median and range)	60	30-100
Tumor type		
Colon	6	8.9
Rectosigmoid	7	10.4
Head and neck	11	16.4
Lung	15	22.4
Bladder	7	10.4
Other sites	21	31.3
Tumor stage		
Disseminated	43	64.2
Local	3	4.5
Locoregional	21	31.3
Pain type		
Mixed	22	32.8
Neuropathic	9	13.4
Somatic	21	31.3
Visceral	15	22.4
ESS		
I	27	40.3
II	13	19.4
III	27	40.3

Abbreviation: ESS, Edmonton Staging System.

percent), disorientation (12 percent), hallucinations (8 percent), nausea (8 percent), and constipation (6.7 percent). The intensity of these AEs was not reported (Table 2).

The most common drugs used for OR were morphine (36 ORs; 48 percent), fentanyl (18 ORs; 24 percent), and transdermal buprenorphine (10 ORs; 13.3 percent). The most common pre-OR drug was fentanyl (38 cases; 50.7 percent). The most common switch was from fentanyl to morphine (27 ORs; 36 percent) (Table 3).

There was no change in the median MEDD of the drugs used pre-OR (120 mg [range, 20-4000 mg]) and on day 7 post-OR (120 mg [10-3600 mg]).

Effectiveness of OR

OR was associated with a statistically significant decrease ($p < 0.001$) in both AP and BTP intensities, as well as in the number of episodes of BTP (Table 4). OR was considered effective in 57 ORs (75.4 percent) for AP and in 42 ORs (57.8 percent) for BTP. In 63 cases, the pre-OR pain scores were ≥4 (moderate or severe pain)[32,33] for AP. In those patients with moderate or severe pain, 32 (50.9 percent) achieved a post-OR score <4 (mild pain)[32,33] for AP and 20 (32.3 percent) achieved such scores for BTP.

Among patients in whom the OR was effective (57 ORs), there were no significant differences between pre-OR and post-OR MEDD ($p < 0.520$). Similarly, no significant increase was observed between the pre-OR and post-OR dose ($p < 0.128$) in patients whose BTP intensity decreased by ≥2 points.

Side effects of OR

The total number of recorded AEs in all 75 ORs was 107 (1.4 AEs per OR). It is notable that in 40

Table 2. Changes in toxicities from initial opioid and postrotation opioid

Previous opioid	Toxicity pre-OR	New opioid	Toxicity post-OR
Fentanyl	Constipation	Morphine	None
Fentanyl	Somnolence, confusion	Oxycodone	None
Buprenorphine	Nausea and vomiting, constipation	Fentanyl	Nausea, constipation
Morphine	Myoclonus	Methadone	Somnolence, confusion, myoclonus, hallucinations
Fentanyl	Somnolence, myoclonus, hallucinations	Methadone	Confusion, constipation
Fentanyl	Somnolence, confusion, myoclonus, hallucinations	Methadone	Somnolence, hallucinations, myoclonus
Fentanyl	Confusion, hallucinations	Methadone	Nausea and vomiting
Methadone	Somnolence, confusion, hallucinations	Fentanyl	None
Fentanyl	Confusion, hallucinations	Methadone	None
Methadone	Somnolence, confusion	Morphine	None
Oxycodone	Nausea	Meperidine	Nausea, constipation
Morphine	Nausea and vomiting, constipation	Fentanyl	Confusion, myoclonus
Buprenorphine	Somnolence, confusion, myoclonus	Morphine	None
Morphine	Somnolence, confusion, nausea and vomiting, constipation	Buprenorphine	None
Fentanyl	Confusion	Morphine	None
Oxycodone	Nausea and vomiting	Morphine	None
Fentanyl	Somnolence, confusion, hallucinations, nausea	Morphine	Confusion, nausea, constipation, xerostomia
Fentanyl	Somnolence	Buprenorphine	None

Table 3. Drugs used in OR							
Previous opiate	New opiate used in OR						
	Mor	Bup	Fen	Oxy	Mep	Mtd	Total
Mor	0	6	10	0	0	2	18
Bup	6	0	7	0	0	0	13
Fen	27	3	0	1	0	7	38
Oxy	1	0	0	0	1	0	2
Mtd	2	1	1	0	0	0	4
Total	36	10	18	1	1	9	75
Abbreviations: Mor, morphine; Bup, buprenorphine; Fen, fentanyl; Oxy, oxycodone; Mep, meperidine; and Mtd, methadone.							

Table 4. Effectiveness of the ORs			
	Day 0	Day 7	p
Median [range] NRS average pain	7.00 [0-10]	3.00 [0-8]	<0.001
Median [range] NRS breakthrough pain	8.00 [0-10]	4.00 [0-10]	<0.001
Median [range] NRS breakthrough pain episodes/day	3.00 [0-10]	1.00 [0-5]	<0.001
Median [range] MEDD	120 [20-400]	120 [10-3600]	ns
Abbreviations: NRS, Numerical Rating Scale; MEDD, morphine equivalent daily dose; and ns, not significant.			

ORs (41 percent), no AEs were reported. The most common side effects involved the gastrointestinal tract (constipation made up 29 percent of events, followed by nausea and vomiting, at 27 percent of events), followed by somnolence (13 percent). Overall, 96 AEs (89.7 percent) were classified as grades 1 and 2 on the CTCAE intensity scale.

DISCUSSION

The main aim of this study was to assess the effectiveness of OR to manage cancer pain. In the 75 ORs that were performed, AP intensity decreased by ≥2 points in more than three fourths of patients. Similarly, BTP intensity also decreased after OR, although only in 57 percent of cases; even so, the number of BTP episodes decreased significantly after OR. Taken together, the findings described here seem to suggest that OR is both safe and effective in the management of both general and breakthrough cancer pain.

Several observational studies have been conducted to assess OR in patients with cancer pain. De Stout et al.[23] retrospectively analyzed the clinical histories of 191 patients admitted to a palliative care unit (PCU). In the 111 ORs that were performed, mean pain scores improved significantly, from 4.4 ± 2.3 to 3.6 ± 2.0 ($p < 0.004$). Müller-Busch et al. also published a notable prospective, follow-up study involving 412 patients who were admitted to hospital and later attended at an outpatient clinic.[34] The authors found that OR led to a reduction in pain intensity in all patients.

An important issue regarding OR is that no uniform criteria have yet been established to define the effectiveness of OR for pain control. Most published studies consider OR to be effective when opioid-related AEs have improved (ie, diminished). Ashby et al.[24] prospectively evaluated the effect of opioid switching on the incidence and severity of AEs in patients with advanced cancer in a PCU. Those researchers observed that, of 55 ORs performed in 49 patients—including both opioid

switches and changes in the route of administration—total or partial improvement was achieved in the control of confusion (72 percent), nausea and vomiting (68 percent), and drowsiness (53 percent), with good pain control in 47 of 49 patients.

In recent years, several authors have begun to redefine the notion of successful OR. Rather than evaluating the success of OR in terms of a reduction in AEs, some authors, like Mercadante et al.,[35] consider OR successful for pain control only if the intensity of pain has decreased to at least 33 percent of the preswitch value, while Gatti et al.[36] consider pain control successful when NRS scores have decreased by at least 50 percent compared to the baseline value. Farrar et al.[37,38] consider opioid treatment to be effective when there is a decrease of ≥2 points in the pain NRS 0-10.

On the basis of the work by Farrar et al., we adopted a similar criteria, in which we consider OR to be effective when the NRS scores decrease by ≥2 points. Based on these criteria, more than 3 of 4 rotations in our study were successful. Furthermore, AP decreased from moderate/severe to mild pain in more than half of the cases. These data are similar to those reported in previous studies,[23,24,27,34,39] although, as abovementioned, interstudy comparison is difficult due to the wide variety of methods used to evaluate OR effectiveness.

We analyzed whether this improvement in AP was due to an increase in opioid dosage during the first week after OR. However, we found no significant differences between pre-OR and post-OR AP regardless of whether the dose had increased or not. This result suggests that changing the opioid dose does not affect the effectiveness of most ORs, whereas simply switching opioids might provide effective AP improvement by itself. The same finding is true for pre-BTP and post-BTP. When the dose was increased after OR, we did not observe any significant improvement in BTP. However, this finding has to be taken with caution, as the number of ORs for BTP was small. Nevertheless, the finding is of interest and merits further study.

Although most studies evaluate changes in AP following OR, most previous studies[23,24,27,34,39] do not address the effectiveness of OR for BTP control, in contrast to the present study. We found that OR is effective in decreasing the intensity of BTP, with pain reduced from moderate/severe to mild in one third of the cases. Furthermore, the number of BTP episodes per day also decreased.

No previous studies have evaluated the opioid-related AEs that arise after OR. In our study, few AEs developed and the ones that did arise were not severe and mostly comprised gastrointestinal disturbances, which usually occur during opioid treatment. These data suggest that OR is a safe and well-tolerated procedure. It bears noting that, in patients who underwent OR due to AEs, opioid-induced neurotoxicity (somnolence, myoclonus, and disorientation) was the main type of AE, whereas post-OR, the most common type of AE was gastrointestinal in nature.

Overall, more than 10 percent of patients required more than 1 OR. Although we did not evaluate which factors were associated with the need for more than 1 OR. Mercadante et al.[27] reported that the need for multiple ORs was associated with poor pain control and the presence of AEs. As in most other studies, the most commonly used opioids were morphine and fentanyl.[23,24,27,34,39] Methadone was relatively infrequent in our study, most likely because radiation and medical oncologists do not typically prescribe this drug.

Finally, the design of this investigation is worth further mention. This was a multicenter study involving specialists from several different medical specialities (palliative care, medical oncology, and radiation oncology services). Kloke et al.[39] also conducted a multicenter study, but only palliative care services were invited to take part. We believe that our approach may provide a better overview of OR in a variety of real-life settings.

Study limitations

The main limitation of this study is its descriptive nature. As a result, variability in the use of opioids and OR techniques was likely large due to the diversity of participating clinical services. Nevertheless, this did not appear to affect results, as we analyzed episodes independently of where they occurred and used the same protocol and equianalgesic table for ORs.[6,29] Another limitation is the lack of data on the intensity of the pre-OR adverse effects. Had this information been available, we could have compared pre-OR and post-OR AE intensity. Given that a secondary objective of the study was to assess the presence of AEs after OR, it would have been useful to record pre-OR side effects.

One interesting piece of information not included in the study protocol would have been

the length of time on the initial opioid before OR, as perhaps variations (eg, shorter or longer) in the duration of opioid use would have resulted in a different response.

Patients were urged to report changes in medication prescribed by other healthcare professionals. No changes were recorded. However, it is possible that unrecorded changes could have occurred; thus, leading to missing data.

In most cases in which OR was performed, the most common initial drug was a fentanyl patch, with other opioids accounting for the remaining cases. Given the predominance of fentanyl, it may be difficult to extrapolate our results to patients on other opioids.

CONCLUSION

Generally, a controlled, progressive increase in opioid doses—tailored to the individual patient—is the recommended strategy to achieve good pain control while minimizing the development of drug tolerance and AEs.[4,40] However, on the basis of the findings of our study, we believe that OR offers clinicians another viable option for managing difficult-to-control pain, including BTP. These proposals are in line with the recommendations of Kloke et al.[39] and Collin et al.,[41] who noted that a certain percentage of ORs are performed without first attempting an increase in opioid dosage for appropriate analgesic control. Nevertheless, in some patients with poor pain control,[42] it may be better to initiate early OR after an appropriate dose increase without waiting for the appearance of side effects because these effects would worsen pain and make further complicate the AE status.[43,44] Indeed, it is recommended that OR or other noninvasive techniques be performed before tolerance and toxicity issues arise. Furthermore, our data suggest that OR is a safe procedure, with side effects that are specific to the opioids used, and a negligible percentage of severe or very severe AEs.

Although we believe the findings presented here are relevant, some unanswered questions remain. For example, we do not know which drug is the most effective for OR or which is the, preferred first-line drug. Similarly, the optimal timing of OR remains unclear. All of these factors need to be addressed, including an accurate definition of OR, assessment of its effectiveness, and conversion ratios between opioids.

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APPENDIX

ROTODOL INVESTIGATORS AND THEIR AFFILIATIONS

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