Eur J Vasc Endovasc Surg (2010) **39**, 774–778

Pain Management in Peripheral Arterial Obstructive Disease: Oral Slow-Release Oxycodone Versus Epidural L-Bupivacaine

B.G. Samolsky Dekel [a,*], R.M. Melotti [a], M. Gargiulo [b], A. Freyrie [b], A. Stella [b], G. Di Nino [a]

[a] *Department of Surgery and Anaesthesiology Sciences, Head Prof. GF Di Nino, Anaesthesiology Section, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy*
[b] *Department of Surgery and Anaesthesiology Sciences, Head Prof. GF Di Nino, Vascular Surgery Section, University of Bologna, Bologna, Italy*

Submitted 5 December 2009; accepted 23 February 2010
Available online 23 March 2010

KEYWORDS
Pain management;
Peripheral Arterial Obstructive Disease;
Epidural;
Opiates;
Oxycodone

Abstract *Objectives:* To compare the effectiveness of oral slow-release oxycodone (group OX, $n = 18$) with that of epidural L-bupivacaine (group LRA, $n = 13$) for the control of moderate/severe pain of advanced-stage peripheral arterial obstructive disease (PAOD) patients.
Design: Observational and retrospective analysis of advanced stage and hospitalised PAOD patients treated for pain management for at least 7 days prior to surgery or discharged from the hospital without surgery.
Methods: The outcome measures were pain intensity using the visual analogue scale under static, (VASs) and dynamic (VASd) conditions; vital signs, treatment side effects and patient satisfaction.
Results: In both groups, pain control was satisfactory and VAS scores median were VASs < 3 and VASd < 4; under dynamic conditions, pain control was better in the LRA group ($p < 0.01$). Against few and transient side effects, most patients ($n = 30$) found both pain treatments good or excellent. Results should be confirmed by studies with larger samples.
Conclusions: In the perioperative setting, the epidural infusion of local anaesthetics, such as L-bupivacaine, is an effective technique for pain control in PAOD patients; for patients with contraindication for this technique or for non-surgical or outpatients, slow-release oxycodone is suggested as a possible alternative for the control of severe pain in these patients.

* Corresponding author. Tel.: +39 051 6363087; fax: +39 051 6364333.
E-mail address: boaz.samolskydekel@unibo.it (B.G. Samolsky Dekel).

1078-5884/$36
doi:10.1016/j.ejvs.2010.02.016

Peripheral arterial obstructive disease (PAOD) of the lower limbs is a frequent multifactorial condition that progressively gives rise to ischaemic pain of the affected limb. It primarily affects the adult male population and is often associated with smoking, hypertension, diabetes, ischaemic coronary disease and carotid artery atherosclerosis. The prevalence of PAOD increases with age from 4.3% of individuals older than 40 years to 35% in those older than 85 years.[1,2] Epidemiological forecasts claim that 27 million of individuals in Europe and in North America will suffer from PAOD in the following years.[3] Symptoms may include deficit of the sexual function, intermittent claudication at various limb levels and at various walking distances, and, in some cases, severe pain at rest and gangrene. About 25% of the patients with intermittent claudication will deteriorate further, 5% will require treatment of revascularisation or the administration of vasoactive drugs and about 2% will have to undergo major amputation.[4]

About 50% of the patients with PAOD complained of symptoms other than intermittent claudication: moderate to severe pain is the most frequent.[5] Symptoms of PAOD at advanced stage negatively affects the patient's quality of life (QOL) and the consequent incapacity induces serious clinical, social and economic costs, especially among individuals who are at a productive age.[6–8] When pain becomes continuous and associated with pre-atrophic and atrophic signs, a feeling of constraint and annoying cramping of increasing intensity is located in the ischaemic muscles; at other times, patients may report hot burning or stabbing sensations of various intensity. Such feelings are almost exclusively located at the anterior part of the foot (sometimes at the forefoot) and are associated with dystrophic signs of progressive aggravation of the arterial insufficiency known as 'evolved intermittent claudication'.

Besides specific therapeutic approach to the underlying disease and its sequels,[9] it is evident that aggressive pain treatment for PAOD patients is essential. Severe chronic pain treatment should include strong opiates[10] given systemically or the use of loco-regional analgesia (LRA) techniques via the epidural route. The epidural route however, is not always feasible. Besides long-term treatments, an epidural catheter is contraindicated in patients with impaired coagulation and platelet aggregation, in the presence of anatomical barriers at the vertebral column or the patient's denial.

The purpose of this study was to compare the effectiveness of the administration of oral slow-release oxycodone with that of LRA for the control of moderate-to-severe pain of advanced-stage PAOD patients.

Methods

This observational and retrospective study was based on the analysis of data stored at the acute pain service (APS) database and from the patients' clinical charts. The APS is run by an anaesthesiology consultant and residents and its activity is integrated with that of the surgical wards and, in particular, with that of vascular surgery. APS members participate in the daily rounds of these wards and also deliver pain management assistance to surgical or non-surgical patients with pain. This assistance includes both pain evaluation 3 times daily and the prescription and the monitoring of invasive or non-invasive pain treatments. All the evaluations and the applied treatments are recorded in the APS database.

Inclusion criteria in the study were advanced-stage PAOD patients (3°—4° stage of Fontaine) >18 years of age, who, over a period of 1 year, were hospitalised in the vascular surgery ward and reported moderate-to-severe lower limb pain, which was not controlled by mild opiates (i.e., codeine or tramadol associated or not with paracetamol) and who were taken in hand by the APS for pain management for at least 7 days prior to surgery or to hospital discharge without surgery.

The APS pain management protocols for such patients were the epidural administration of 4 ml L-bupivacaine 0.25% every 6 h (group LRA) or, in the presence of contraindications for the positioning of an epidural catheter, the oral administration of slow-release Oxycodone with the initial dose of 10—20 mg twice daily (group OX). In case of poor pain control, the prescribed rescue doses were an epidural bolus of 4 ml L-bupivacaine 0.25% up to 3 times in 24 h (group LRA) or an oral tablet of the association of oxycodone 5 mg and paracetamol 325 mg, up to six times in 24 h (group OX).

The intensity of pain was evaluated three times daily from the moment of application of pain treatment until surgery or until hospital discharge without surgery. Pain management continuity was guaranteed to all patients: those who underwent surgery were followed, post-operatively, by the APS team, while those who were discharged without surgery, were periodically monitored by the pain management outpatient office.

Pain intensity was evaluated using the visual analogue scale [VAS, 0 ('no pain') to 10 ('most intense pain I can imagine')] both under static (VASs, patient lies still on the bed) and under dynamic conditions (VASd, during limb movement). Pain management objectives were to maintain pain intensity within VASs ≤ 3 and VASd ≤ 4. At the same time, we also recorded non-invasive arterial blood pressure (AP), heart rate (HR), respiratory rate (RR), the presence of treatment side effects, and the degree of patient satisfaction of the pain management treatment. In particular, expected side effects were motor block, hyposthenia or hypoaesthesia, signs of neurological or cardiac local anaesthetic toxicity; or opiates side effects, such as sedation (using the Ramsey 5-item scale), respiratory depression, nausea, vomiting, itching or constipation. Finally, patient satisfaction was estimated before hospital discharge or surgery using a 4-item category scale: insufficient, sufficient, good or excellent.

Ethics

The study was a routine activity and therefore no specific authorisation and approval were required from the Hospital Ethics Committee. The study was conducted according to the Helsinki declaration and the International Association for the Study of Pain (IASP) Guidelines for Pain Research in Animals and Humans. All participants were personally and thoroughly informed by the ward and the APS physicians on the applied pain management regimen and gave informed consent.

Data Presentation and Statistical Analysis

All analyses were conducted using StatView for Windows (SAS Institute Inc., Cary, NC, USA). Pain intensity scores were reported as median, interquartile range, 5% and 95% centiles and range. Differences between VAS scores were analysed using a paired *t*-test. Statistical significance was defined as $P < 0.01$.

Results

Over 1 year, group LRA ($n = 13$) and group OX ($n = 18$) patients were identified and included in the study. Table 1 shows these patients' demographic characteristics, Fontain stage, the applied pain treatment and the clinical outcomes of both groups. Except for the pain treatment used, the two groups were homogeneous.

Figure 1 shows box and whisker plots of the median, interquartile range and range of the VAS scores during the 21 pain evaluations. In group LRA, the median score of VASs was 2.0 (interquartile range, 1.0—2.0; 5% and 95% centiles, 0.0 and 3.0, respectively; range, 0.0—8.0) and that of VASd was 3.0 (interquartile range, 2.0—3.0; 5% and 95% centiles, 1.0 and 4.0, respectively; range, 0.0—10.0). In group OX, the median score of VASs was 2.0 (interquartile range and 5% and 95% centiles, 0.0 and 3.0, respectively; range, 0.0—9.0) and that of VASd was 3.0 (interquartile range, 2.0—5.0; 5% and 95% centiles, 2.0 and 6.0, respectively; range, 0.0—9.0).

Statistically significant differences between the two groups were observed under dynamic conditions as, under these conditions, pain control was better in the LRA group ($P < 0.01$).

Treatment side effects were relatively rare in both groups. In group OX, only one patient reported transient (<24 h) somnolence (Ramsey scale 2—3); in group LRA, one patient reported lower limb hypoaesthesia and hyposthenia in the first 4 h after the positioning of the epidural catheter.

Rescue dose was administered in five patients ($n = 3$ in group LRA and $n = 2$ in group OX). In these patients, treatment was hence optimised as follows: in the LRA group, L-bupivacaine 0.25% boluses were increased from 4 to 5 ml (12.5 mg); in the OX group, the daily dose of oxycodone was doubled. Finally, most patients ($n = 30$) found the applied pain treatment good or excellent and only one patient described it as sufficient.

Discussion

Pain management in the growing substantial population of patients with PAOD is a major issue both in the perioperative setting and for outpatients. 'Non-surgical' pain management modalities for these patients may include neurolytic or radiofrequency lumbar sympathetic block and electrical spinal-cord stimulators. These modalities tend to be effective in and indicated for ischaemic conditions with a major vasospastic component. Often, patients' compliance, availability of technology, operator experience and comfort level influence the selection of one of these expensive modalities. Our findings suggest that epidural analgesia with boluses of L-bupivacaine provides robust pain relief under both static and dynamic conditions. Alternatively, for long-term treatments and for patients who cannot be treated with 'non-surgical' pain management modalities or epidural analgesia, oral slow-release oxycodone may provide optimal analgesia under static conditions and to lesser extent, yet satisfactory, under dynamic conditions.

Pain management in PAOD patients with severe ischaemic pain of the lower limbs is scantily addressed. In these patients, the two major objectives of treatment are: (1) to prevent ischaemic attacks and (2) to improve QOL. When making medical decisions, it is generally accepted that patients are as much concerned by QOL as by life expectancy, particularly with regard to chronic diseases for which the aim of therapy is not only to treat the disease but also to relieve pain or restore function.[8]

Chronic severe pain, like that of PAOD patients, is characterised by three elements: (1) lack of direct or exclusive relationship between the extension of the tissue lesion and pain intensity; (2) a personal and subjective experience with a variable association of sensory, emotional and cognitive factors; and (3) the concomitant activation of peripheral nociceptors due to tissue lesion (i.e., nociceptive pain) and

Table 1 Demographic characteristics, Fontain stage, pain treatment and clinical outcomes split by the study groups. OS, oral; bid, twice daily; SR, slow release; IR, immediate release.

Group	*n*	Female/ Male	Age	Fontain stage		Analgesia applied		Clinical result	
		n	Mean (±SD)	III	IV	Main treatment	Rescue dose	Surgery	Discharge
LRA	13	3/10	74.4 (±9.5)	$n = 4$	$n = 9$	Epidural boluses: L-Bupivacaine 0.25% 4 ml/6 h	L-Bupivacaine 0.25% 4 ml, max 3 boluses/24 h	$n = 7$	$n = 6$
OX	18	3/15	73.3 (±6.3)	$n = 6$	$n = 12$	OS bid: Oxycodone SR Daily mean dose: 27.8 (±12.2) mg	(Oxycodone 5 mg + paracetamol 375 mg IR) max 6 times/24 h	$n = 8$	$n = 10$
Total	31	6/25	73.8 (±7.7)	$n = 10$	$n = 21$			$n = 15$	$n = 16$

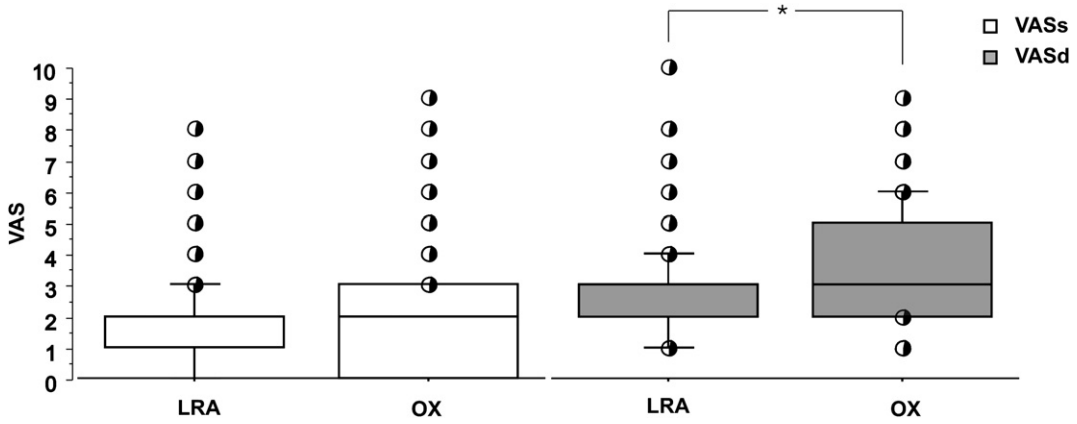

Figure 1 Box and whisker plots of the median, interquartile range and range of the VAS scores during the 21 pain evaluations. *$P < 0.01$.

the aberrant activity or pathology of the nervous system (i.e., neuropathic pain). In PAOD patients, both types of pain may co-exist given the presence of both tissue and peripheral nervous system lesions due to the frequent ischaemia and, eventually, to diabetic neuropathies. Evidence shows that opiates give good response rate in nociceptive and neuropathic pain states in patients with chronic pain of non-cancer origin.[11,12]

Chronic severe pain compromises physical activity, sleep and sexual activities and leads to changes in mood, reduced self-esteem and negative feelings, such as despair; in addition, pain causes alterations in patients' family, work and leisure relationships. The intensity and frequency of pain may exceed its function as a protective indicator and may seriously compromise the QOL of affected individuals.[6–8]

Physiological responses to postoperative pain may alter organ functions (cardiovascular, pulmonary, coagulation, endocrine, gastrointestinal, central nervous system, etc.). Pain alleviation not only improves patients' comfort, but also may minimise perioperative stress response, physiological responses and postoperative organ dysfunction, assist postoperative nursing and physiotherapy, enhance clinical outcome and potentially shorten the hospital stay.

Potent postoperative analgesia, especially by the epidural route, may be associated with reduction in incidence and severity of many perioperative dysfunctions.[13–15] Epidural analgesia using local anaesthetics is the best technique for decreasing postoperative stress after lower abdominal or lower limb surgery. Analgesia using either epidural or high doses of opiates may improve some cardiac variables such as tachycardia and ischaemia, but does not change the incidence of severe cardiac complications in patients with pre-existing high cardiac risk. For patients undergoing vascular or orthopaedic surgery, epidural analgesia can improve clinical outcome by preventing the development of arterial or venous thrombo-embolic complications[16] as during LRA, unlike during general anaesthesia, the fibrinolytic system is not inhibited.[17]

In this study, we used L-bupivacaine for LRA. L-Bupivacaine has been developed to offer a safer alternative to bupivacaine, having the desirable blocking properties of racemic bupivacaine with a greater margin of safety due to its reduced toxic potential. In particular, L-bupivacaine provides a long-lasting block with a clinical profile characterised by a fine differentiation between sensory and motor blocks. This is particularly useful when recovery of motor function and early mobilisation is important to accelerate postoperative recovery. The reduced toxic potential of L-bupivacaine is strongly supported by animal and volunteer studies. It is characterised not only in higher plasma concentrations and doses before signs of systemic toxicity occur, but also in no cardiovascular toxicity or only minimal signs of cardiac effects after central nervous system toxicity occurs in case of either overdosing or unintended intravascular injection.[18]

Guidelines for chronic pain management consider opiate medications as effective analgesics with a well-established role in the management of severe pain.[11] These potent medications require a thorough understanding of their risks and benefits, along with a basic skill set to assess and manage risk and titration. With appropriate diagnosis and monitoring, they are tools that can be employed effectively with other management techniques for the treatment of acute and chronic pain.[19] Morphine is considered as the gold standard of opiate prescription for severe pain. Among the newer available opiates, compared to oral morphine, oral slow-release oxycodone, at equal analgesic doses, is thought to have a better biodisposability, fewer itching, hallucinogenic and other side effects and the ability to control painful diabetic neuropathies.[20] Evidence shows that post-retropubic prostatectomy pain control with oral slow-release oxycodone is preferable to epidural analgesia.[21] In the present study, the initial dose of oxycodone was 10—20 mg twice a day; titration to higher doses was based on the rescue dose consumption in 24 h.

The main limitations of the study are its retrospective nature and the small sample size. Such limitations impose caution before taking the study's results as definitive. However, the study results may be considered sufficient to warrant further prospective and randomised studies to verify the generalisation of the findings as (1) both treatments appear to be satisfactory with the only advantage for the LRA group under dynamic conditions and (2) the statistical difference between the groups was of high significance ($P < 0.01$), thus limiting the risk of type II error. Further

investigation should address also the issue of side effects and major complications of each treatment modality.

In the perioperative setting, in accordance with the literature, the epidural infusion of local anaesthetics, such as L-bupivacaine, is an effective analgesia technique for the control of pain in PAOD patients; alternatively, for patients with contraindication for this technique, non-surgical or outpatients and for long treatments, a strong opiate with a known anti-neuropathic pain activity, such as oral slow-release oxycodone, may be further studied as a valid choice for the control of severe pain in PAOD patients.

Conflict of Interest

All authors disclose no financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

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