



Leg edema from intrathecal opiate infusions

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Despite the increasing popularity of intrathecal infusions to treat patients with long-term non-cancer-related pain, this therapy is not without serious side-effects. Five out of 23 patients who had intrathecal infusions of opiates for longer than 24 months developed leg and feet edema. As predisposing factors, cardiovascular disease, deep venous thrombosis, peripheral vascular disease, and venous stasis of the lower extremities were considered. Every patient who developed pedal and leg edema after the implantation of an infusion pump was also found to have leg edema and venous stasis prior to the time when the pump was inserted. This complication was severe enough to limit their physical activity, and to produce lymphedema, ulcerations and hyperpigmentation of the skin. Reduction of the edema occurred when the dose of the opiate was decreased, and in two cases in which the infusion was discontinued, there was almost complete resolution of the syndrome. It appears that the pre-existence of pedal edema and of venous stasis is a relative contraindication to the long-term intrathecal infusion of opiates in patients with chronic non-cancer pain. © 2000 European Federation of Chapters of the International Association for the Study of Pain.

KEYWORDS: edema, infusion, intrathecal, opiates.

INTRODUCTION

Edema in the lower extremities has been casually reported to occur in a few patients with permanently-implanted pumps for the continuous intrathecal infusion of opioids (Winkelmuller and Winkelmuller 1996). The incidence of this complication and the possible etiological factors were analyzed in a group of 23 patients with chronic, non-malignant pain, in whom five developed lymphedema.

METHODS

Twenty-three adult patients with one to three previous lumbar spine fusions having resulted

in pseudoarthrosis and arachnoiditis were followed from 24 to 62 months after the placement of permanently-implanted pumps (Medtronic Inc., Minneapolis, MN, USA) for the administration of intrathecal opioids. Specifically, the occurrence, duration, and severity of pedal and/or leg edema were documented. Other related complications such as scoriations, ulcerations, infections, and/or erythema were also recorded. After the onset of the symptoms, an ultrasound of the venous and arterial vascular systems of the lower extremities was taken in all of the five patients. In addition, in all patients, a pump myelogram was performed 8–20 months post-implantation, when the occurrence of pedal and leg edema were noted. The pre-existence of possible etiological factors, including hypertensive cardiovascular disease (HCVD), deep venous thrombosis (DVT), peripheral vascular disease (PVD), and venous stasis of the lower extremities (VSLE)

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TABLE 1. Pre-existing conditions to lymphedema

	Number (%)	Before implanation				After implantation			
		HCVD	DVT	PVD	VSLE	HCVD	DVT	PVD	VSLE
Patients with pedal & leg edema	5 (22%)	2	1	0	5	3*	2**	0	5
Patients without pedal & leg edema	18 (78%)	3	0	0	0	3	1**	1	0

*One patient had thrombosis of the middle cerebral artery.

**With negative ultrasound but acute swelling with tenderness and redness along the popliteal and femoral veins.

HCVD=Hypertensive Cardiovascular Disease

DVT = Deep Venous Thrombosis

PVD = Peripheral Vascular (Arterial) Disease

VSLE = Venous Stasis of the Lower Extremities

were retrospectively determined (Table 1). Lower extremity edema was rated as: (+) 'slight' with swelling of the feet only; (++) 'mild' when there was swelling of the feet and ankles; (+++) 'moderate' when the edema was up to the lower half of the leg (Fig. 1); and (++++) 'severe' when marked swelling was evident up to the knees, with trophic skin changes and pigmented discoloration and/or ulcerations along the signs of venous insufficiency (Fig. 2).

Treatment

All five patients received diuretics, including hydrochlorothiazide (50 mg), alternating every 3

months with furosemide (20 mg) daily. They were also fitted with elastic stockings; however, frequently, there was non-compliance due to heat intolerance, which is usually exhibited in patients with arachnoiditis (Aldrete and Zapata, 1998). In two of them, scoriations of the skin appeared (Fig. 2), eventually leading to small cutaneous ulcerations requiring topical care with saline and hydrogen peroxide soaks, as well as a cream prepared with 20% phenytoin in aloe vera. Gradual compression pumps were applied in three individuals with only temporary improvement. The most effective treatment was leg elevation and gradual dose reduction to about 50% of the medication infused, necessitating supplementation of the subarachnoid opiate with oral hydrocodone



FIG. 1. Bilateral leg edema with brownish pigmentation in a patient treated with intrathecal infusion of opiates for 28 months.



FIG. 2. Patient after 54 months of intrathecal infusion of opiates with bilateral leg edema showing dermatitis, hyperpigmentation, and ulceration in both legs.

TABLE 2. Response to treatment for edema of the lower extremities

Patient	Leg elevation	Elastic stockings	Diuretics	Reduction of dosage
Case #1	IN-C	IN-C	I	I*
Case #2	IN-C	IN-C	I	I
Case #3	IN-C	I	NI	I*
Case #4	IN-C	IN-C	I	I
Case #5	IN-C	IN-C	I	I

*Infusion was discontinued.

I = Improved

NI = Not Improved

N-C = Non-compliant

to provide the patients with acceptable analgesia. Although leg elevation improved the edema, it considerably reduced the patient's physical activities (Table 2). One patient insisted on having the pump removed, and in a second patient, the pump's battery ran out; in both of them, the edema and the trophic changes of the skin subsided (Fig. 3).

RESULTS

Five out of the 23 patients (21.7%) with permanently-implanted pumps for intrathecal opioid administration developed pedal and leg edema 6 months after the beginning of the treatment. Three patients were receiving oxymorphone from 6–13 mg/day, and two others received morphine sulfate (12–16 mg/day); only commercially-available, preservative-free solutions were used. Four cases were bilateral (Fig. 1) and one case was unilateral. One patient showed slight edema, another had mild edema, the other three patients had a severe type of edema (Fig. 2). In two of these patients, one leg had greater swelling than the other leg. Arterial and venous ultrasound studies failed to show arterial occlusion or deep venous thrombosis (DVT), ruling them out and implying lymphedema. Retrospectively, before the pump implantation, it had been noticed that one patient had severe edema and prior episodes of DVT; four others had slight edema; in every instance, the pedal and leg edema increased after implantation. Pump myelograms showed the intrathecal catheters to be in their proper position, and no other anatomical abnormality was found that could explain the edema in the legs and feet. No correlations with HCVD or PVD were found.



FIG. 3. The legs of the patient shown in Fig. 2, 10 months after discontinuing the intrathecal infusion of opiates. The edema and hyperpigmentation have been markedly reduced.

DISCUSSION

Chronic lymphedema is a low output failure of the lymphatic circulation, when the centripetal transport of lymph is reduced (Goldstein, 1985). Lymphedema is classified as primary and secondary. Primary lymphedema may be subdivided into: a) congenital (when present at birth); b) praecox (when it becomes evident in the teens or twenties); and c) tarda (when it develops after age 25) (International Society of Lymphology, 1995). Secondary lymphedema, in general, is due to another disease process, such as neoplasia, infection, radiation, insect bites, surgical excision, and motor paralysis (Goldstein, 1985). The factors that might have predisposed to the occurrence of lymphedema in this group of patients are shown in Table 1.

In 1996, according to Winkelmuller and Winkelmuller (1996), sweating and peripheral edema were the most unpleasant side-effects shown by patients treated with intrathecal opioids. Though controversial, it appears that opiates may produce a sympathetic blockade of a minor degree (Durrett and Lawson, 1989; Kirnö *et al.*, 1993) when infused into the intrathecal space, therefore, it could exacerbate pre-existing foot and leg edema in patients with a prior history of varicosities, peripheral-venous insufficiency, and DVT. In our patients, treatment with diuretics, elastic stockings, and gradual compression pumps only partially improved their pedal edema.

The sympathetic nervous system usually controls arterial and venous capacitance, preventing undue venous dilation and blood pooling during the erect posture (Goldstein, 1985; Durrett and Lawson, 1989). Local anesthetics, when deposited into the spinal canal, interrupt sympathetic outflow, thereby producing venous pooling (Bridenbaugh and Greene, 1988), supposedly from peripheral vascular dilation (mostly venous). The scarcity of reports concerning this complication during opiate intrathecal infusion appears unexplained. In 1996, Winkelmuller and Winkelmuller (1996) reported edema in the lower extremities in 6.1% of their patients, however, it was observed in 21.7% of our patients; in 1985, Paice *et al.* (1996) reviewed 429 patients from a multicenter retrospective study and found leg edema in 11.7% of them.

In view of this limited but consistent data, it appears indicated to identify the presence of varicose veins, to evaluate the competence of venous valves and the presence of pedal edema in patients who are being considered as candidates for permanent intraspinal opiate therapy. Specifically, the Brodie-Trendelenburg test (Goldstein, 1985) has been recommended to determine venous lower extremity insufficiency. This potential complication should also be discussed with patients who are candidates to receive long-term intrathecal opioid infusions.

The occurrence of severe pedal leg swelling, and in some cases breaks in the integrity of the skin (Fig. 3), producing seeping lesions that prevent ambulation, appears to be a serious handicap in the achievement of the goals of treatment in these patients. This complication seems to be influenced by dose, and although it is not life-threatening, it nevertheless further increases the extent of the patient's disability.

The development of lymphedema in five ambulatory patients who had permanent pumps implanted for the infusion of intrathecal opioids is described. The predisposing factors appear to be previous leg edema and venous insufficiency, which are most likely exacerbated by opioid dose-dependent vasodilation. Pre-existing leg venous insufficiency and edema may be relative contraindications for the continued use of intrathecal opioids in patients with chronic pain.

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