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Etilefrine use in the management of post-operative chyle leaks in thoracic surgery

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Abstract

Etilefrine, a sympathomimetic drug, was used 11 times in 10 patients with thoracic ($n = 8$) or abdominal ($n = 2$) chyle leak occurring after thoracic surgical procedures. It was given as a 4.2–5 mg/h intravenous infusion. During the 11 etilefrine administrations, three patients had total parenteral nutrition, three had enteral nutrition, three had oral fat-free diet and medium-chain triglyceride supplementation, and two were fed orally without restriction. Daily chyle flow output decreased in all but one patient who was reoperated. Chyle flow output did not decrease relevantly in one patient who was reoperated. Chylothorax recurred after reoperation and etilefrine then induced significant output decrease. In another patient, etilefrine was stopped despite significant output reduction because of interactions with other sympathomimetic drugs used for heart failure. The mean etilefrine treatment duration was 6.4 days (range 4–7). The mean daily output was from 740 ml before etilefrine infusion to 183 ml on the seventh day of etilefrine use. By inducing contraction of the smooth muscle fibres present in the wall of the main thoracic chyle ducts, etilefrine can be considered as a useful adjunct in the management of post-operative chyle leak.

Keywords: Thoracic surgery; Oesophagectomy; Chylothorax; Chyloperitoneum; Conservative treatment

1. Introduction

Any thoracic procedure may be accompanied by a laceration of the main thoracic duct. Depending on leak localization, thoracic duct lesions result in chylothorax or less frequently chyloperitoneum. Post-operative chylothorax occurs in less than 1% of thoracic procedures and its prevalence has ranged from 0.5 to 4% [1]. Although some patients present with insidious leaks or non-specific chest discomfort or dyspnoea, diagnosis of post-operative chyle leak is easily suspected when there are increased losses on chest or abdomen drainage or a recurring pleural or peritoneal collection of fluid. Diagnosis is confirmed by biochemical examination of the effusion showing increased triglyceride (chylomicrons) and lymphocyte levels.

Until recent years, there was considerable controversy over the management of post-operative chyle leak. Since mortality rate is estimated between 30 and 50% with conservative management of post-operative cases (efficient drainage, total parenteral nutrition, fat-free diet together with medium-chain triglyceride supplementation) [1,2], most authors currently agree that surgery should be undertaken [3], especially in patients with high-output chyle leaks [1]. There is, however, no consensus whether surgery should be performed early or after a test period of controversial duration. Etilefrine, an α- and β-adrenergic sympathomimetic drug used in postural hypotension, has been proposed as an additional conservative method [4,5]. We here report our experience in managing post-thoracotomy chyle leak by using etilefrine in a series of 10 patients (11 etilefrine administrations).

2. Patients and methods

From January 1995 to June 2002, all patients with significant chyle leak occurring after oesophagectomy in

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our Department of Surgery in the Lille University Hospital were included in the present study. Either chyle leaks with a daily output of at least 250 ml or chyle leaks with a duration of at least 7 days were considered significant. Baseline characteristics of selected patients are presented in Table 1. Eight patients (six males, two females) presented with either post-operative chylothorax ($n = 6$) or chyloperitoneum ($n = 2$). In one patient, chylothorax recurred after reoperation for persistent chylothorax and etilefrine was used twice, after oesophagectomy and after reoperation. Etilefrine was therefore used nine times in eight patients. Out of these patients, three were previously described in a case report [6]. Following this report, two surgeons (I.P. and C.P.) asked for complementary details about etilefrine use and managed two additional male patients with post-operative chylothorax according to our recommendations. These two cases were included in the previous eight patient-group. For the 10 patients, the mean age was 51 years (34–66). Chyle leak was suspected because of increased and/or prolonged drainage of a thoracic or an abdominal effusion, and confirmed by biological examinations (increased levels of chylomicrons and/or lymphocytes in the effusion).

Following chyle leak diagnosis, a test conservative management was performed including persistent effusion drainage. Etilefrine was given as a 5 mg/h intravenous infusion except in patient 3 who was given reduced doses because of poor tolerance (increased heart rate and blood pressure). In this patient, a maximal 4.2 mg/h dose was administered after a gradual dose increase. For all patients under etilefrine treatment, daily chyle flow output was recorded to assess etilefrine efficacy. Adverse effect occurrence was also recorded. When chyle flow resolution was obtained, etilefrine infusion was halved and then stopped over 24–48 h.

3. Results

In the 10 patients, chyle leak was diagnosed because of increased chylomicrons or lymphocytes in a thoracic or abdominal persistent effusion (Table 1). The mean time of chyle leak diagnosis was 8.9 days after the surgical procedure (range 4–23). During the 11 etilefrine administrations, other therapeutic modalities to control chyle leak were effusion drainage in all patients and total parenteral nutrition in three patients (Table 2). Three patients had enteral nutrition through a jejunal feeding tube. The five remaining patients were fed orally. Of these, three had a fat-free diet together with medium-chain triglyceride supplementation while the other two were fed normally without restriction.

The mean daily chyle flow output was recorded under etilefrine infusion (Fig. 1). The day before etilefrine introduction, the daily output ranged from 80 to 1830 ml. Three patients (patients 4, 7 and 10) had a daily output higher than 1 l. Only patient 6 had a daily output less than 250 ml (i.e. 80 ml/day) but was included in the study because the chyle leak persisted for more than 1 week. Under etilefrine treatment, daily chyle flow output decreased in all but one patient (Table 2). In this patient (patient 1), no significant change was observed during a 5-day-long etilefrine administration. Clipping of the thoracic duct was performed 2 days after etilefrine infusion withdrawal (on the 15th post-operative day) via right thoracotomy and induced chyle flow resolution within 2 days. Patient 4 had a 1180 ml chyle flow output before etilefrine introduction. Besides chylothorax, he post-operatively had heart and respiratory failure. Etilefrine was given on the 23rd post-operative day. Daily chyle flow output significantly decreased and reached 205 ml on the fourth day of treatment. However, etilefrine had to be stopped because of interactions with other sympathomimetic drugs used for heart failure (dopamine, dobutamine). A right thoracotomy was performed on the 27th post-operative day and an accessory thoracic duct, that was not identified during the first surgical procedure, was clipped. Chyle leak resolution was obtained the following day. In patient 10, only minimal chyle flow output decrease was observed after a 7-day-long etilefrine administration. The patient was then reoperated through right thoracotomy and laparotomy.

Table 1
Baseline characteristic of patients with post-operative chyle leak treated with etilefrine

Patient	Gender	Age	Surgical procedure	Chyle leak	Post-operative day of chyle leak diagnosis	Chyle flow output (ml)
1	Female	62	Subtotal oesophagectomy and total gastrectomy	Chylothorax	8	360
2	Female	51	Subtotal oesophagectomy	Chylothorax	11	260
3	Male	34	Right inferior pulmonary lobectomy	Chylothorax	5	250
4	Male	52	Subtotal oesophagectomy	Chylothorax	23	1180
5	Male	44	Subtotal oesophagectomy and total gastrectomy	Chyloperitoneum	10	440
6	Female	50	Subtotal oesophagectomy	Chyloperitoneum	7	80
7	Male	66	Subtotal oesophagectomy	Chylothorax	4	1450
8	Male	58	Subtotal oesophagectomy	Chylothorax	4	250
9	Male	37	Subtotal oesophagectomy	Chylothorax	4	400
10	Male	55	Subtotal oesophagectomy	Chylothorax	8	1635
			Thoracotomy and laparotomy for chyle leak	Chylothorax	14	1830

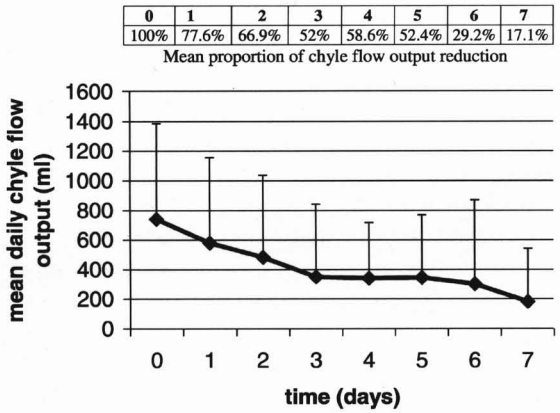

Fig. 1. Evolution of the mean daily chyle flow output under etilefrine treatment. The percentage of reduction was calculated as the ratio of daily output as compared to the daily output before etilefrine introduction.

Chylothorax was found to result from an intraperitoneal leak (around the origin of the left gastric artery) that refluxed in the thorax across the oesophageal hiatus. The chyle leak was clipped but chylothorax recurred on the 14th post-operative day. Etilefrine was then administered again during 7 days and induced partial but significant chyle flow output decrease. Chylothorax then stopped spontaneously on the 24th post-operative day.

Overall, etilefrine administration was successful in seven of the 10 patients. In two patients, an insignificant decrease was observed and reoperation was performed in order to clip again the thoracici duct. In one patient, etilefrine administration was interrupted because of interaction with other sympathomimetic drugs. The patient was reoperated and an accessory thoracic duct was clipped.

For the 10 patients (11 etilefrine administrations), the mean daily output before etilefrine infusion was 740 ml (Table 1). Etilefrine was administered for a mean 6.4 day duration (range 4–7). Fig. 1 shows daily chyle output evolution under etilefrine treatment. Despite the absence of chyle flow reduction in patients 1 and 10 (first etilefrine use), a progressive decrease of the mean daily output was observed (Fig. 1). It felt from 740 to 183 ml on the seventh day of etilefrine use ($P = 0.0128$, Wilcoxon matched-pairs signed-rank test). A mean 83%-reduction was therefore observed on the seventh day of etilefrine use.

Side-effect related to etilefrine use was observed in only two patients. In patient 4, interactions with other sympathomimetic drugs required etilefrine infusion withdrawal. In patient 3, a clinically relevant increase in heart rate and blood pressure was observed under etilefrine treatment but only needed dose adaptation without withdrawal. No other side-effect was noted using etilefrine infusion in the remaining patients.

4. Discussion

Post-operative chyle leak is a life-threatening complication. Although obviously depending on the amount, rate and duration of chyle loss, it can induce significant local, metabolic and immunological adverse effects [7]. Local effects include compression of the ipsilateral lung with subsequent shortness of breath, and mediastinal shift that in turn can impair contralateral lung and heart functions. Continued fluid loss also induces protein, fat, vitamin and electrolyte depletions that require consequent nutritional support. At last, cell-mediated immunity and humoral responses are compromised. Although all authors agree that such devastating complications require prompt control of the chyle leak, there is still considerable controversy over the appropriate management strategies [7].

One of the conservative management is simple close drainage of the pleural cavity, which evacuates chyle,

Table 2
Outcome of patients with post-operative chyle leak treated with etilefrine

Patient	Chyle flow output (ml)	Nutrition during etilefrine use	Other treatments	Etilefrine treatment	Output outcome	Chest or abdomen drainage* (days)	Hospital stay* (days)
1	360	Oral	Middle-chain triglycerides	5 days (10th–14th)	No decrease, reoperation	33	35
2	260	Enteral	None	7 days (18th–24th)	Significant decrease	25	26
3	250	Parenteral	None	7 days (11th–17th)	Significant decrease	24	26
4	1180	Parenteral	None	4 days (23th–26th)	Significant decrease, reoperation	39	63
5	440	Oral	Middle-chain triglycerides	7 days (10th–16th)	Significant decrease	17	18
6	80	Oral	None	5 days (9th–13th)	Significant decrease	15	17
7	1450	Enteral	None	7 days (5th–11th)	Significant decrease	13	15
8	250	Oral	None	7 days (5th–11th)	Significant decrease	13	14
9	400	Enteral	None	7 days (6th–12th)	Significant decrease	15	16
10	1635	Parenteral	None	7 days (9th–15th)	Insignificant decrease, reoperation	57	59

*From the first thoracic surgical procedure.

re-expands lung and obliterates the potential pleural space. Repeated or continuous drainage can, however, result in huge fluid losses with increased metabolic and immunological adverse effects. All daily losses should therefore be replaced intravenously. Withdrawal of oral fat intake reduces chyle flow. Total parenteral nutrition is the preferred method of nutritional support. However, substituting dietary fat with medium-chain triglycerides also reduces the quantity and total duration of chyle loss while permitting continued oral diet. Inhibition of gastrointestinal secretions by somatostatin analogues also proved to be effective in reducing chyle flow and may be considered as a useful adjunct [8].

For surgical management, the traditional approach is open thoracic, abdominal or cervical ligation of the thoracic duct [2]. Intraoperative leak identification may be favoured by pre-operative administration (orally or via nasogastric tube) of cream or fat meal potentially stained by methylene blue or Sudan black [9]. When the site of chyle leak cannot be identified, fibrin glue and/or talc can be sprayed in the mediastinal or abdominal region suspected for leakage [10]. Recently, thoracoscopy gained popularity, because of easy manageability, and reduced post-operative pain, morbidity and hospital stay for both thoracic duct ligation [11] and fibrin glue or talc administration [10].

Either conservative or surgical strategies must be considered in light of the specific aetiological type of chylothorax and the patient's general condition [7]. In particular, because of high mortality, aggressive management is classically recommended in post-operative chylothorax [12]. For example, the mortality rate for post-oesophagectomy chylothorax may reach as high as 50% with conservative management [2]. Timing to reoperation remains, however, controversial. Some authors advocate early thoracic duct ligation [13] whereas others plead for a conservative management test period reserving surgery for chylous leak persistent for more than 2 weeks or greater than 1 l per day for more than 5 days [12,14]. Recent authors suggested that the test period can be shortened to a few days [3].

Etilefrine has seldom been reported as an interesting adjunct in the management of post-operative chyle leak [4–6]. Although including a small number of patients, the present study suggests that its systematic use in the setting of a short test period is deserved to be considered. We feel that etilefrine should be added to the conservative measures. As an α-adrenergic sympathomimetic drug, it has been used in the treatment of postural hypotension and priapism [15]. Besides other sympathomimetic actions, it causes smooth muscle contraction. Since thoracic duct and main lymphatic vessels contain smooth muscle fibers [6], it probably decreases chyle flow output by reducing main lymphatic vessel diameters. Its action is not constant since one patient in our series did not exhibit any change in chyle output whereas another only experienced minimal decrease. Those two patients required reoperation for iterative clipping of the thoracic duct. This inefficacy did not depend on chyle flow output since a significant decrease was observed in two other patients with daily output higher than 1 l. We encountered limitations in etilefrine use in two patients. In one of them, dose adaptation and progressive dose increase were required because he experienced increased heart rate and blood pressure. A therapeutic effect was observed despite reduced doses. In another one, to allow reliable evaluation of the resuscitation measures used in the context of post-operative heart failure, etilefrine administration was stopped because interactions with other sympathomimetic drugs were thought to occur. None of the other side effects classically related to etilefrine (headache, nervousness, flushes, palpitations) [15] were noticed. It is worthy to note that etilefrine should be interrupted when surgery is indicated and halogenic drugs planned to be used for general anaesthesia since severe heart arrhythmia can occur.

In conclusion, our data favour the use of etilefrine in the management of post-operative chyle leaks. We feel therefore that etilefrine can be considered as a useful adjuvant to the strategy that proposes a test conservative management and reserves surgery in case of refractory chyle leakages. It should be systematically added to other conservative measures when a test period is chosen.

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