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CLINICAL RESEARCH

Single-centred experience with levosimendan in paediatric decompensated dilated cardiomyopathy

Expérience monocentrique du levosimendan dans les myocardiopathies dilatées pédiatriques en insuffisance cardiaque terminale

CrossMark

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Summary
Background. — Children with dilated cardiomyopathy in advanced heart failure may spend a long time awaiting heart transplantation. Consequently, mechanical circulatory support is sometimes required as a bridge to transplantation. Levosimendan, a positive inotropic agent, has been reported to be safe and efficient for the treatment of paediatric heart failure.
Aims. — To report our experience with levosimendan in children with decompensated dilated cardiomyopathy.
Methods. — Paediatric patients with dilated cardiomyopathy on the transplant waiting list and with criteria for mechanical support were included in this single-centred retrospective study. Each patient received at least one 24-hour infusion of levosimendan before mechanical circulatory support was considered. Biological and echocardiographic data were analysed.

Results. — Six patients were included over a 24-month period. The median age was 25.5 months (7.7—34.2 months); 82 infusions were performed. Median B-type natriuretic peptide concentration decreased significantly between days 0 and 2 (2443 ng/L [1458—3819 ng/L] vs 1358 ng/L [1025—2534 ng/L]; $P = 0.003$). While only a trend was noted in left ventricular ejection fraction improvement ($P = 0.054$ by Simpson's method and $P = 0.068$ by the Teicholz method), the subaortic velocity time integral rose significantly between days 0 and 8 (12.8 cm/s [10—14.5 cm/s] vs 15.3 cm/s [14.3—16.9 cm/s]; $P = 0.041$).

Conclusions. — Levosimendan seems to improve haemodynamics in children with decompensated dilated cardiomyopathy; repeated infusions may delay the need for mechanical circulatory support while awaiting heart transplantation. This therapeutic agent should be systematically considered in this setting, in addition to conventional inotropic drugs.

Résumé
Contexte. — Les enfants qui ont une cardiomyopathie dilatée en insuffisance cardiaque terminale et qui sont sur liste de transplantation cardiaque sont susceptibles d'attendre longtemps un greffon. Ainsi, le recours à une assistance mécanique circulatoire est parfois nécessaire lorsque l'état du patient ne lui permet plus d'attendre. Le levosimendan, inotrope positif, a précédemment été rapporté sûr et efficace pour le traitement de l'insuffisance cardiaque de l'enfant.

Objectifs. — Rapporter notre expérience du levosimendan chez des enfants avec cardiomyopathie dilatée en insuffisance cardiaque terminale.

Méthodes. — Ont été inclus, dans une étude rétrospective monocentrique, tous les enfants ayant une cardiomyopathie dilatée sur liste de transplantation cardiaque et avec des critères d'assistance circulatoire mécanique. Avant la mise sous assistance, chaque patient a au moins reçu une cure de levosimendan de 24 h. Les paramètres biologiques et échocardiographiques ont ensuite été analysés.

Résultats. — Six patients ont été inclus sur une période de 24 mois. L'âge médian était de 25,5 mois (7,7—34,2). Quatre-vingt-deux infusions ont été réalisées au total. Le taux médian de BNP diminuait significativement entre j0 et j2 (2443 ng/L [1458—3819 ng/L] contre 1358 ng/L [1025—2534 ng/L] ; $p = 0,003$). Alors que seule une tendance à l'amélioration était notée pour la fraction d'éjection ventriculaire gauche ($p = 0,054$ par la méthode de Simpson et $p = 0,068$ en Teicholz), l'ITV sous-aortique augmentait significativement entre j0 et j8 (12,8 cm/s [10—14,5 cm/s] contre 15,3 cm/s [14,3—16,9 cm/s] ; $p = 0,041$).

Conclusion. — En considérant la possibilité de perfusions itératives, le levosimendan semble améliorer l'état hémodynamique de ces patients. Afin d'attendre au mieux un greffon cardiaque, le levosimendan devrait être systématiquement considéré dans cette indication et en association avec les traitements habituels.

Background

Dilated cardiomyopathy (DCM), with an annual incidence of 0.57 to 0.72 per 100,000 children, is the most common form of paediatric cardiomyopathy [1,2]. Indeed, within the Pediatric Heart Transplant Study group, DCM accounts for 83% of all paediatric cardiomyopathy [3]. This disease is caused by a variety of conditions: idiopathic, familial, neuromuscular disorders, post-myocarditis, chemotherapeutic drugs, metabolic disorders and ventricular non-compaction. Despite the use of conventional therapies, the prognosis for DCM has not changed appreciably in recent decades [4]. DCM accounts for > 50% of indications for paediatric heart transplantation [5], which remains the gold standard therapy for end-stage heart failure. Because the wait for a transplant may be long, the use of mechanical circulatory support (MCS) is sometimes required as a bridge to transplantation, despite the use of conventional inotropic drugs.

Levosimendan, being a calcium sensitizer of cardiac troponin and an adenosine triphosphate-sensitive potassium agonist, improves myocardial contraction [6] and allows relaxation of the vascular smooth muscle cells [7], which are responsible for coronary vasodilation. Maximal haemodynamic effects of levosimendan have been shown to occur 1—3 days after starting the infusion and are sustained for at least a week. Although this positive inotropic agent

has been widely investigated in adults [8], only a few studies have tested its use in children [9]. Nevertheless, levosimendan has been shown to be safe and effective after paediatric cardiac surgery [10–12], especially in case of low cardiac output syndrome [13–16]. These results have encouraged many European centres to use levosimendan routinely to prevent postoperative low cardiac output syndrome [17]. In a population of children with DCM and chronic heart failure, the use of levosimendan was rarely reported [18,19], despite a shared perception of efficacy among physicians who tried it [20]. Finally, one study has advocated rotative inotrope therapy, with levosimendan infusions, in children with decompensated heart failure [21].

Because of these promising results, levosimendan has been used frequently in our institution in the past few years. The aim of this study was to retrospectively evaluate the effects of levosimendan in children with DCM who were on the waiting list for heart transplantation.

Methods

Study design

This was a single-centred retrospective study. Over a period of 24 months (February 2010–January 2012), we enrolled all children with DCM in end-stage heart failure and listed for heart transplantation. Inclusion criteria were: patients aged < 18 years, in stage D according to the last paediatric classification of heart failure proposed by the International Society of Heart and Lung Transplantation [22], who were on the waiting list for heart transplantation, with, initially, indications for MCS, and who received at least one infusion of levosimendan before they had either a transplant or MCS. Indications for mechanical assistance—extracorporeal membrane oxygenation (ECMO) or any ventricular assist device (VAD)—were: left ventricular ejection fraction (LVEF) < 30% (by the Teicholz method and Simpson's method); metabolic acidosis with a pH $\leq$ 7.30; and B-type natriuretic peptide (BNP) concentration > 500 ng/L, despite continuous conventional intravenous inotropic support (milrinone and epinephrine). Patients with DCM but without indications for MCS were excluded from the study. Biological and echocardiographic data were collected and analysed according to the levosimendan infusions. Continuation of conventional inotropic therapies was at the discretion of the physicians. All of our patients with DCM receive angiotensin-converting enzyme inhibitors, beta-blockers and diuretics.

Infusions of levosimendan

Because the use of levosimendan (Simdax®; Orion, Espoo, Finland) is limited to exceptional circumstances in France (a temporary certificate of use is delivered by the public health authorities), physicians had to obtain an informed consent form from the parents before the infusions. The patients received at least one continuous infusion of levosimendan at a dose of 0.2 μg/kg/min for 24 hours, without any loading dose. Use of further infusions was at the discretion of the physicians, on the basis of clinical, biological (BNP concentration) and echocardiographic arguments.

Serum analysis

Measurements of BNP concentration were requested by physicians according to their own practice. Depending on the size of the patient, venous samples were collected either in 1.3 mL K_3 EDTA microtubes (Sarstedt, Nümbrecht, Germany) or in 4 mL K_3 EDTA BD Vacutainer® tubes (Beckton Dickonson, Franklin Lakes, NJ, USA). Blood samples were immediately transported to the laboratory after collection. BNP concentrations were measured in whole blood by a fluorescent immunoassay method (Biosite Diagnostic, San Diego, CA, USA) on a UniCel® DxI 800 system (Beckman Coulter, Fullerton, CA, USA). Measurements were completed within 2 hours of sample collection.

Echocardiographic evaluation

Echocardiographic acquisitions were performed in the same manner three paediatric cardiologists experienced in echocardiography. Thus, for each patient, a single echocardiogram was acquired daily by the practitioner who was present in the unit. All images were acquired using a Vivid i® system (GE Healthcare, Little Chalfont, UK). A 3S-RS or a 7S-RS transducer was used, depending of the age of the patient. LVEF was determined using two methods: the Teicholz method, using the M-mode in a parasternal long-axis view; and the Simpson's method, in a two-dimensional apical four-chamber view. The subaortic velocity time integral was determined from an apical five-chamber view using the Doppler mode. Each echocardiographic acquisition was transferred and recorded on our institution's network, and was later reviewed, using EchoPAC® software (GE Healthcare, Little Chalfont, UK), by a fourth cardiologist who was blinded to the outcome of the patients. Because of the retrospective design of the study, no variability analysis (intra- or intervariability) was performed.

Statistical analysis

All the data, which were collected at the time of each infusion of levosimendan, were pooled to analyse the evolution of the different variables. All values are expressed as the median and first and third quartiles. We used a Mann-Whitney U test to compare values. The software package SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations. P values < 0.05 were considered significant.

Ethics

The study was approved by our local ethics committee. A written consent form was not required, according to French law, because the studies were part of the regular management of the children. No examinations were performed only for the purpose of the study.

Results

During this period, of the 91 patients followed in our centre for paediatric DCM, only six were eligible for MCS and were included. Table 1 summarizes the characteristics of

Table 1 Patient characteristics at the time of the first infusion of levosimendan.

Patient no.	Sex	Weight (kg)	Aetiology of DCM	Age at diagnosis	Age at inclusion (months)	Inotropic support	pH	BNP (ng/L)	Serum creatinine (μmol/L)	LVEF[a] (%)	Subaortic VTI (cm/s)	Normal subaortic VTI according to age (cm/s)[b]
1	M	11.4	Immunological (maternal lupus)	Prenatal	37	Milrinone	7.28	6671	38	20	10.8	20.3—26.0
2	M	62	Idiopathic	15 years	182	Milrinone	7.25	3421	85	15	12.8	23.3—29.7
3	F	4	Idiopathic	2 months	2	Milrinone	7.30	4819	28	18	11.7	13.1—18.6
4	M	14.3	Idiopathic	2 years	26	Milrinone	7.26	1415	38	24	12.5	20.1—25.6
5	M	3.3	Idiopathic	2 months	2	Milrinone	7.30	11,878	44	22	13	13.1—18.6
6	F	10	Post-myocarditis	2 years	25	Dobutamine	7.27	2243	23	21	11.5	20.1—25.6

BNP: B-type natriuretic peptide; DCM: dilated cardiomyopathy; F: female; LVEF: left ventricular ejection fraction; M: male; VTI: velocity time integral.

[a] Simpson's method.

[b] Values of normal aortic VTI are expressed as range ± 1 Z-score; from Pees et al. (2013) [34].

Table 2 Outcome of patients who received iterative infusions of levosimendan.

Patient no.	No. of infusions	Time between first infusion and MCS/HTx (days)	Time at home between first infusion and MCS/HTx (days)	Conventional inotropic support withdrawal	No. of infusions of levosimendan that enabled withdrawal	MCS (type)	Outcome
1	13	221	54	Yes	1	Yes (VAD, 18 days)	HTx
2	5	28	0	No	NA	No	HTx
3	16	120	8	Yes	9	Yes (ECMO, 5 days; + VAD, 13 days)	HTx
4	11	108	41	Yes	2	Yes (VAD, 3 months)	HTx
5	5	258	152	Yes	2	No	Death (sepsis)
6	32	570	381	Yes	3	No	HTx

ECMO: extracorporeal membrane oxygenation; HTx: heart transplantation; MCS: mechanical circulatory support; NA: not applicable; VAD: ventricular assist device.

the study population. The median age at inclusion (i.e. at the time of the first infusion of levosimendan) was 25.5 months (7.7—34.2 months) and the median weight was 10.7 kg (5.5—13.5 kg). The sex ratio was 2:1 (four boys). At inclusion, all patients had a central venous line and inotropic support. Four patients had a skin-tunnelled central venous catheter (patients 1, 3, 5 and 6). None of the patients had respiratory support (invasive or non-invasive). The aetiology of DCM was idiopathic for four patients, immunological as a result of maternal systemic lupus for one patient and secondary to a myocarditis (Epstein-Barr virus) for the last patient. The immunological cardiomyopathy had been suspected since the foetal stage because of the detection of an atrioventricular block associated with ventricular dysfunction in the presence of lupic maternal antibodies. Autopsies of the explanted hearts confirmed the absence of myocarditis lesions in the three patients with idiopathic DCM and who could have been transplanted.

Infusions of levosimendan

A total of 82 24-hour infusions were performed. The number of infusions per patient is reported in Table 2. After the first infusion, and for all the patients, it was always possible to delay the need for MCS because the criteria were no longer met.

Effect on BNP concentration

Results are reported in Table 3. While BNP concentrations decreased after the infusion of levosimendan, the lowest BNP concentration was observed 48 hours after the beginning of the treatment. The difference between the BNP concentrations was significant only between day 0 and day 2 ($P = 0.003$) (Fig. 1). The difference between day 0 and day 8 was not significant ($P = 0.506$).

Effect on echocardiographic variables

Results are reported in Table 3. LVEF assessed either by the Teicholz method (TM mode) or by Simpson's method did not improve significantly after the infusion of levosimendan. Only a trend was noted between day 0 and day 8 for each method ($P = 0.068$ and $P = 0.054$, respectively). In contrast, the subaortic velocity time integral improved significantly between day 0 and day 8 (Fig. 2).

Outcomes

Five patients were finally transplanted. Despite iterative infusions of levosimendan, three of these patients had MCS before transplantation ('bridge to transplantation') because the criteria were met again. Patients 1 and 4 had a ventricular assist device (VAD) (Berlin Heart Excor®, GmbH, The Woodlands, USA) immediately and patient 3 had ECMO as first intention before having a VAD 5 days later (Table 2). Although clinical, biological and echocardiographic variables were stable after five infusions of levosimendan, patient 5 died in our unit as a result of staphylococcal sepsis (infection of the central venous catheter). For all of the patients, median event-free survival (mechanical assistance support, transplantation or death) was 170 days (111—249 days). When considering only the use of MCS (three patients), median survival was 120 days (114—170 days). No adverse events were reported or attributed to the use of levosimendan.

Discussion

As levosimendan has been shown to be effective in the treatment of heart failure in different clinical situations, we have used it routinely in our unit, for many years, in children with decompensated cardiac disease. Because this agent does not increase oxygen consumption of cardiomyocytes,

Table 3 Daily evolution of B-type natriuretic peptide concentration and echocardiographic variables after infusions of levosimendan.

	Day 0	Day 1	Day 2	Day 3
BNP (ng/L)				
Median	2443	1733	1358	1781
IQR	1458–3819	933–2758	1025–2534	1175–3502
n	82	72	60	45
LVEF (%) (Teicholz)				
Median	21	20.3	24	21.5
IQR	18.7–24.9	17–29	20.3–29.3	15.5–26.1
n	58	33	22	10
LVEF (%) (Simpson)				
Median	21	19	24	24.8
IQR	17.7–27.5	15.3–22	20–27	21.5–26.1
n	40	21	13	5
Subaortic VTI (cm/s)				
Median	12.8	12.4	12	11
IQR	10–14.5	11.1–13.5	10.4–14.8	9.2–12.3
n	69	35	23	15
	Day 4	**Day 5**	**Day 6**	**Day 7**	**Day 8**
BNP (ng/L)					
Median	1684	1745	1730	1722	1808
IQR	1185–3595	1119–3476	1276–3942	1279–3389	1341–3832
n	55	46	54	47	21
LVEF (%) (Teicholz)					
Median	23	23.2	21.5	21	23.1
IQR	18.3–24.5	19.8–24.2	18.3–25.6	18.7–25.8	20–29.6
n	11	11	18	16	9
LVEF (%) (Simpson)					
Median	20.3	23	23.2	23.7	28
IQR	13.5–25.1	16.5–27	17.2–27.2	21.1–29.9	28.6
n	7	9	14	11	7
Subaortic VTI (cm/s)					
Median	10.9	11.5	12.3	12.9	15.3
IQR	9.5–12.1	8.7–13.1	10–15	9.1–14.3	14.3–16.9
n	14	19	21	18	35

BNP: B-type natriuretic peptide; IQR: interquartile range; LVEF: left ventricular ejection fraction; VTI: velocity time integral.

it appears to be an emerging tool for the treatment of paediatric heart failure [9,18–20]. Although Suominen et al. reported the good perception of physicians who used levosimendan in a paediatric population [20], no previous study has analysed the effect of levosimendan on biological and echocardiographic variables in a population of children with DCM in end-stage heart failure. We believe that levosimendan, by exercising beneficial effects on cardiac function, is efficient in delaying the need for MCS. Indeed, criteria for MCS were no longer met, temporarily at least, after the first use of levosimendan. When considering mechanical assistance and heart transplantation, our patients benefited from > 3 additional months without the need for MCS while waiting for a transplant (although some required ECMO or a VAD, ultimately). While the wait for a heart transplant (inherently uncertain) may be long, this gain in time is extremely valuable for patients. As morbidity and mortality have been shown to be correlated to the duration of

mechanical assistance, every day 'free from assistance' is highly beneficial [23].

BNP concentration is well correlated with New York Heart Association class in children with heart failure (either in the context of congenital heart disease or cardiomyopathy), and this biological marker has been found to be useful in monitoring these patients [24]. In adults with advanced heart failure, levosimendan has been shown to be more effective than furosemide infusion at improving BNP concentration [25]. We also demonstrated that BNP was significantly decreased after an infusion of levosimendan. For our patients, this effect was greatest on day 2 after the infusion. In contrast, there was no significant improvement in LVEF, which may be a reflection of the small size of our cohort. Variability in M-Mode and two-dimensional measurements, which can reach 15% [26], may also explain our findings. The aortic velocity time integral, which has been found to be reliable for the extrapolation of cardiac
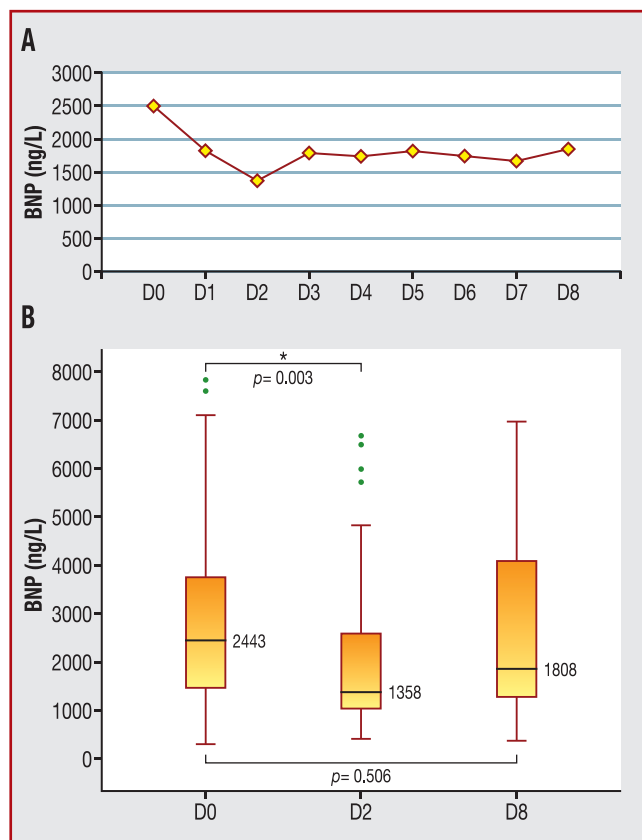
Figure 1. Daily evolution of B-type natriuretic peptide (BNP) concentration according to the infusion of levosimendan in a population of children with dilated cardiomyopathy in end-stage heart failure. A. The evolution of BNP concentration shows a minimal value on day 2 after the infusion and a persisting effect until day 8. B. The difference in BNP concentration is significant between day 0 (D0) and day 2 (D2). Boxes represent first and third quartiles, horizontal lines represent medians and whiskers indicate 10th—90th percentiles. Circles represent outliers. A Mann-Whitney U test was used to compare the medians.

Figure 2. Daily evolution of subaortic velocity time integral (VTI) according to the infusion of levosimendan in a population of children with dilated cardiomyopathy in end-stage heart failure. The improvement in subaortic VTI value was significant between day 0 (D0) and day 8 (D8) after the infusion. Boxes represent first and third quartiles, horizontal lines represent medians and whiskers indicate 10th—90th percentiles. A Mann-Whitney U test was used to compare the medians.

index in children [27,28], was significantly improved until day 8 after the infusions. This observation is consistent with a previous study that advocated a rotative inotrope therapy involving repeated levosimendan infusions in addition to conventional inotropic agents for children with decompensated heart failure [21]. Because its active metabolite, OR-1896, has a long elimination half-life, levosimendan has a long-lasting effect of few days, making iterative infusions interesting [29]. However, these effects seemed to decrease over the time. Indeed, physicians had the impression that subsequent infusions were less effective after a few months.

In their recent meta-analysis, Delaney et al. showed that, compared with dobutamine, levosimendan improved the survival of adults with acute severe heart failure [30]. However, this finding was probably the result of a higher mortality rate associated with the use of dobutamine, rather than a real reduction in the mortality rate associated with levosimendan. Indeed, compared with placebo, levosimendan did not significantly reduce the mortality rate. Although randomized trials in a general population of adult patients with acute severe heart failure failed to show a correlation between the haemodynamic efficacy
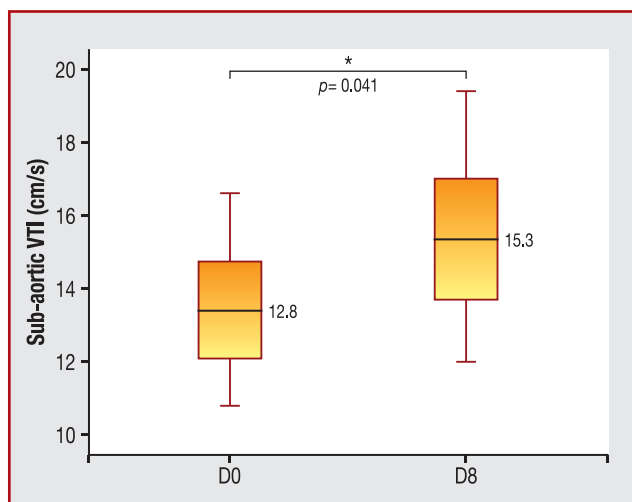
of the drug and a sustained survival benefit, the value of levosimendan in targeted populations (such as DCM in end-stage heart failure) remains to be studied specifically. While randomized trials included patients with both acute and chronic heart failure, only one infusion was performed to compare levosimendan with other inotropic drugs. The heterogeneity of the cohorts seems to be a major pitfall of these studies. The inevitable progression of certain cardiopathies should not be compared with acute and, sometimes, reversible causes of heart failure. Similarly, the treatment may vary according to the disease. Hence, levosimendan should be reused to treat chronic heart failure efficiently, even if there is a potential loss of efficacy over the time. This attenuation of haemodynamic effects was shown previously by Hitz et al., who reported the case of a 14-year-old boy with DCM who was treated successfully with levosimendan until transplantation [31]. Apart from this intra-individual variability in efficiency, which is probably related to the natural course of the heart disease, there is obviously an interindividual variability in levosimendan effects. This difference, observed between patients with the same cardiopathy, allows differentiation between responders and non-responders. In a study that examined the haemodynamic effects of levosimendan in adult patients with borderline right ventricular function before left VAD implantation, a reduction in N terminal pro-BNP concentration of < 25% from baseline values was significantly associated with worse outcomes (caused by severe right ventricular dysfunction) [32]. Moreover, Farmakis et al. showed, in a population of acute decompensated heart failure, that the BNP response to therapy was correlated with survival [33]. Indeed, patients with a BNP change > 58% had a better 6-month survival than patients with a BNP reduction < 58%. Therefore, levosimendan-induced BNP reduction, being an independent predictor of mid-term outcome, may

potentially identify patients who might benefit from a strategy of multiple levosimendan infusions.

Study limitations

The main limitation of our study lies in its retrospective and observational aspect. Indeed, we did not have any control group to compare the evolution of such children without levosimendan infusions. Thus, the decision to use MCS was made by the physicians according to the usual clinical, biological and echocardiographic arguments. Nevertheless, before the beginning of the infusions, all the patients were eligible for MCS. Because our patients were unresponsive to conventional intensive medical management, levosimendan undoubtedly allowed MCS to be delayed. Finally, the small size of our cohort may explain why the median BNP values had large standard deviations. This lack of statistical power is possibly also responsible for the absence of significant LVEF improvement.

There is a lack of randomized controlled studies on the use of levosimendan in children, and further studies are needed to confirm these results. Because there are still no official indications for its prescription in paediatric patients, levosimendan was used as a rescue drug for our children, which means that it was only used in the final stage of the cardiac disease. In DCM, earlier administration may make it possible to further delay the ineluctable decline in cardiac cell properties. To optimize the use of this new therapeutic agent, objective criteria (clinical, biological and echocardiographic) for its delivery remain to be determined.

Conclusion

Levosimendan seems to improve haemodynamics in children with DCM in end-stage heart failure. In such critical patients, the use of this positive inotropic agent facilitates the wait for heart transplantation. Indeed, repeated infusions of levosimendan may allow several months to be spent without the need for MCS. In the context of advanced paediatric heart failure, our study suggests the systematic use of levosimendan, in addition to conventional medications. Further prospective randomized studies are needed to confirm these preliminary results.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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