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Reviews

Cell-Based Therapy Using Umbilical Cord Blood for Novel Indications in Regenerative Therapy and Immune Modulation: An Updated Systematic Scoping Review of the Literature

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A B S T R A C T

Cell-based therapy using umbilical cord blood (UCB) is being used increasingly in novel applications. To balance heightened public expectations and ensure appropriateness of emerging cell-based treatment choices, regular evidence-based assessment of novel UCB-derived therapies is needed. We performed a systematic search of the literature and identified 57 studies (814 patients) for analysis. Sixteen of these studies (353 patients) included a control group for comparison. The most commonly reported novel indication for therapy was neurologic diseases (25 studies, 476 patients), including studies of cerebral palsy (12 studies, 276 patients). Other indications included diabetes mellitus (9 studies, 149 patients), cardiac and vascular diseases (7 studies, 24 patients), and hepatic diseases (4 studies, 106 patients). Most studies administered total nucleated cells, mononuclear cells, or CD34-selected cells (31 studies, 513 patients), whereas 20 studies described the use of UCB-derived mesenchymal stromal cells. The majority of reports (46 studies, 627 patients) described cellular products obtained from allogeneic sources, whereas 11 studies (187 patients) used autologous products. We identified 3 indications where multiple prospective controlled studies have been published: 4 of 4 studies reported clinical benefit in cerebral palsy, 1 of 3 studies reported benefit for cirrhosis, and 1 of 3 studies reported biochemical response in type 1 diabetes), although heterogeneity among the studies precluded meaningful pooled analysis of results. We anticipate a more clear understanding of the clinical benefit for specific indications once more controlled studies are reported. Patients should continue to be enrolled on registered clinical trials for novel therapies. Blood establishments, transplantation centers, and regulatory bodies need to prepare for greater clinical demand.

INTRODUCTION

Although used mainly for transplantation of hematopoietic stem cells in the treatment of blood disorders, cell-based therapies using umbilical cord blood (UCB) are now being used increasingly for novel applications in nonhematopoietic diseases and as a form of cellular regenerative therapy or immune modulation. Indeed, new types of cellular products are emerging using UCB cells as a starting material, including mesenchymal stromal cells, endothelial progenitors, and neural progenitors [1]. We provided an initial scoping review of published studies and ongoing trials in 2013 and described the use of UCB for the treatment of neurologic diseases (eg, spinal cord injury, stroke, traumatic brain injury), diabetes mellitus and other autoimmune conditions, cardiac and vascular diseases, gastrointestinal diseases, and dermatologic diseases [2]. Given the rapid pace of progress in this area, we conducted an updated scoping review and analysis to provide more current insight into the use of UCB for emerging novel indications. In particular, we sought to understand whether increasing numbers of studies were including prospective control groups that would allow for an assessment of efficacy. In the face of increasing hype and elevated public expectations regarding the potential uses of UCB therapy, there is an urgent need to perform regular evidence-based assessments of emerging applications to inform cord blood banking establishments, transplantation centers, and patients, and to avoid the inappropriate use of unproven therapies [3-5].

METHODS

Searching for Relevant Published Trials

We searched for studies that described the use of human UCB to treat patients for nonconventional indications that addressed regenerative therapy

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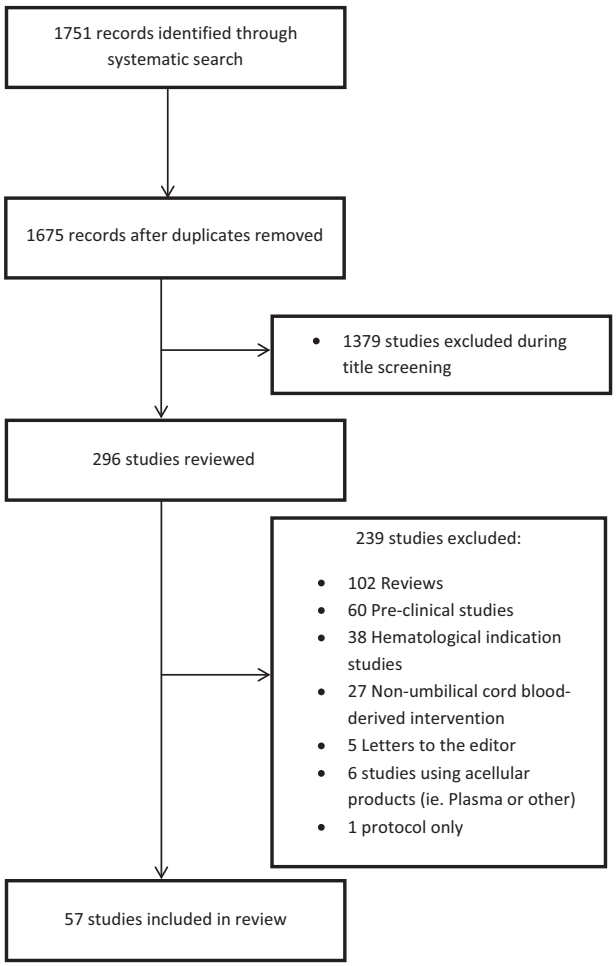

Figure 1. Results of our systematic literature search.

or modulation of immune disorders (Figure 1). A systematic scoping review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6] using MEDLINE and EMBASE (1950 to June 1, 2016), using a previously published search strategy [2]. We also identified any additional literature using Google Scholar and checking bibliographies of included studies.

Information Analysis

All duplicates, editorials and opinion articles, review articles, and studies involving animals and articles that did not involve human UCB were removed. The screening and selection of articles for inclusion and analysis was performed in duplicate (by M.R. and J.A.). All relevant studies were categorized based on disease process (eg, cardiovascular, diabetes, hepatic). Each article was then analyzed for the following parameters: specific disease treated, patient age, geographic region of intervention, relationship of patient to donor of banked cord blood unit (allogeneic or autologous), route of administration of cells, cell product administered, and adverse event reporting. These parameters were then tabulated and described.

RESULTS

Our search strategy initially identified 1751 articles. After duplicates were removed, 1675 articles were screened for relevance, and 296 studies underwent full text review. Of these, 239 were excluded for the following reasons: 102 reviews, 60 preclinical studies, 38 studies in which UCB was given for a standard hematologic indication, 27 studies in which a product not derived from UCB was administered, 5 letters to the editor, and 1 study protocol and 6 studies reported on acellular cord blood-derived products (4 studies using UCB serum, 1 using platelet-derived gel, and 1 using UCB mesenchymal stem cell microvesicles) [7-12]. A total of 57 studies comprising 814 patients were included for final analysis. A total of 16 studies comprising 353 patients were controlled.

The most commonly reported novel indication for therapy was neurologic diseases (25 studies, 476 patients) [13-37]. Cerebral palsy was the disease most frequently studied among this subgroup (12 studies, 276 patients) [13-24]. Other commonly studied indications included diabetes mellitus (9 studies, 149 patients) [38-46], cardiac and vascular diseases (7 studies, 24 patients) [47-53], and hepatic diseases (4 studies, 106 patients) [54-57]. The complete list of disorders studied is provided in Table 1. Of the 57 studies, 43 (75% enrolling 516 patients) reported possible benefit to patients. Thirty-four studies (60%) reported on the presence or absence of adverse events. Of these, 25 studies reported no adverse events, and 9 studies reported minor and/or serious adverse events, which are summarized in Table 2. Postinfusion headaches, fever, nausea/vomiting, and urticaria were reported in multiple patients in several studies; more serious neurologic adverse events, including seizures, subdural and subarachnoid hemorrhage, and intracranial hypotension, occurred less frequently and were associated with interventions for neurologic disorders. Two of 6 patients receiving allogeneic cells for cartilage hair hypoplasia developed acute graft-versus-host disease. Systematic patient-specific data extraction

Table 1
Clinical Studies of Regenerative Therapy or Immune Modulation Using UCB-Derived Cell Transplantation

Disorder [Reference(s)]	Published (Patients), n	Controlled Studies (Patients), n	Studies Reporting Possible Benefit (Patients), n
Neurologic [13-37]	25 (476)*	6 (171)	16 (270)
Cerebral palsy [13-24]	12 (276)	4 (141)	9 (201)
Degenerative conditions [25]	1 (114)	0	0
Traumatic brain injury [26-28]	3 (29)	1 (20)	2 (23)
Stroke [29,30]	2 (14)	0	1 (4)
Spinal cord injury [31-35]	5 (41)	1 (10)	5 (41)
Diabetes mellitus [38-46]	9 (149)	4 (53)	6 (108)
Type 1 [38-42]	5 (68)	3 (29)	3 (27)
Type 2 [43-46]	4 (81)	1 (24)	4 (81)
Cardiac and vascular [47-53]	7 (24)*	1 (12)	7 (24)
Myocardial infarction [47,48]	2 (13)	1 (12)	2 (13)
Hepatic/gastrointestinal [54-57]	4 (106)	4 (106)	2 (55)
Liver cirrhosis [54-56]	3 (81)	3 (81)	1 (30)
Hepatitis B [57]	1 (25)	1 (25)	1 (25)
Muscle/cartilage disorders [58-62]	5 (21)*	1 (11)	5 (21)
Muscular dystrophy [58-60]	3 (15)	1 (11)	2 (12)
Other [63-69]	7 (38)*	0 (0)	7 (38)
Systemic lupus erythematosus [63]	1 (16)	0	1 (16)
Total	57 (814)	16 (353)	43 (516)

* Other indications: amyotrophic lateral sclerosis [36] (1 study, 1 patient); multiple sclerosis [37] (1 study, 1 patient); hypoplastic left heart syndrome [49] (1 study, 1 patient); dilated cardiomyopathy [50] (1 study, 1 patient); diabetic erectile dysfunction [51] (1 study, 7 patients); critical limb ischemia [52] (1 study, 1 patient); basilar artery dissection [53] (1 study, 1 patient); cartilage hair hypoplasia [61] (1 study, 6 patients); articular cartilage damage [62] (not stated); optic nerve hypoplasia [64] (1 study, 2 patients); Leber hereditary optic neuropathy [65] (1 study, 1 patient); wound repair [66] (1 study, 2 patients); chronic discogenic back pain [67] (1 study, 2 patients); bronchopulmonary dysplasia [68] (1 study, 9 patients); and bone nonunion [69] (1 study, 6 patients).