

Bowel/Bladder Sensation and Control in Patients with Spinal Cord Injury Treated with Human Embryonic Stem Cell therapy

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Abstract

Background: Spinal cord injury (SCI) results in long-lasting Locomotor and sensory neuron degeneration. SCI patients suffer from autonomic nervous system dysfunction. Neurogenic bowel and bladder problems are the additional complicating medical problems associated with SCI. The present study evaluated the bowel/bladder sensation and control in patients with SCI after human embryonic stem cell (hESC) therapy.

Methods: This is a retrospective analysis (May 2005-Aug 2012) of 226 SCI patients (mean age-28 years) treated with hESC therapy. Therapy schedule included four treatment phases (T1, T2, T3, T4) lasting 4-6 weeks separated with gap phases (4-8 months). hESCs in an injectable form (cultured and maintained in-house in a xeno product free patented technology) were administered at a dose of 0.25 ml (< 4 million cells) intramuscularly twice daily, 1 ml hESCs (< 16 million cells) every 10 days through intravenous route and 1-5 ml hESCs every 5- 7 days by any of the supplemental routes. The patients with bowel and bladder problems were graded based on their symptoms.

Results: Overall, 200 (81.5% patients had no bowel sensation of fullness or evacuation) and 204 (77.5% had no bladder sensation of filling or voiding) subjects had bowel and bladder sensation problems, respectively; while, 203 (81.5% had no bowel control), and 209 (92.3% had no bladder control) subjects had bowel and bladder control problems, respectively. At the end of therapy, 7 (3.5%) patients reached bowel sensation normalcy, 7 (3.4%) patients reached bladder sensation normalcy, 135 (67.5%) had mild, partial or full sensation of bowel fullness and 155 (76%) patients had mild, partial and full sensation of bladder filling. Similarly, 4 (2%) reached bowel control normalcy, 4 (1.9%) reached bladder control normalcy, 95 (46.8%) had bowel control and 113 (54%) had bladder control. The number of subjects with ASIA grade A was reduced after the therapy.

Conclusion: An improvement in bowel/bladder control and sensation was observed in SCI patients after hESC therapy.

Keywords: spinal cord injury; human embryonic stem cells; bowel/bladder control and sensation problems

Abbreviations: SCI: Spinal cord injury; hESC: Human embryonic stem cells; IEC: Independent ethics committee; IC-SCRT: Institutional committee for stem cell research and therapy; ICMR: Indian Council of Medical Research; i.m: Intramuscular; i.v: Intravenous; TLR: Toll like receptor;

Background

Spinal cord injury (SCI) involves a complex series of pathological events resulting in long-lasting Locomotor and sensory neuron degeneration (Lukovic., *et al.*) [1]. SCI patients suffer from autonomic nervous system dysfunction that can affect bowel/bladder sensation and control (Karlsson) [2]. The spinal cord is a common pathway for transmission of sensory impulses from the bladder and urethra to the ascending and descending nerves. It is considered as a primary reflex center for micturition (Vignes, Deloire and Petry; Xia., *et al.*) [3,4].

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Injury to the spinal cord at tenth thoracic (T10) and the second lumbar (L2) vertebrae results in urinary incontinence and an overactive bladder (Francis). Neurogenic bowel and bladder problems are the additional complicating medical problems associated with SCI (Liu, *et al.*) [5].

It is observed that the patients with complete tetraplegia and paraplegia due to SCI often have a Neurogenic bowel and bladder (Shavelle, *et al.*) [6]. In a study by Liu, *et al.* 46.9% SCI patients had Neurogenic bowel dysfunction that varied from moderate to severe. The subjects with more severe bowel dysfunction had physical disability in their daily living. Around 39% SCI patients with bowel dysfunction suffered major restrictions in social activities (Liu, *et al.*) [5]. In a cross sectional survey by Yammen, *et al.* of 50 adult SCI patients, 43 patients had a history of occasional or regular fecal incontinence. Majority of patients (62%) required 16-30 min to complete the bowel evacuation and half (54%) patients required assistance in bowel evacuation Yammen, *et al.*

Several treatment options such as surgical methods or non-surgical methods involving intermittent catheterization, continuous drainage, drug treatment, Neuromodulation, and bladder training and expansion exist in current clinical practice; however, the efficacy of many of these treatments are unknown and sometimes unreliable (Xia, *et al.* [4]; Chen and Liao) [8]. Although, drugs and manual stimulation helped many SCI patients to achieve an adequate bowel frequency, the risk and occurrence of fecal incontinence, difficulties with evacuation, and need for assistance remain significant problems (Lynch, *et al.*) [9].

Stem cell transplantation, one of the promising technologies has a potential to replace the damaged neurons and re-establish the lost axonal connections. Stem cells provide neuroprotective factors that allow healing and recovery after SCI. Human embryonic stem cells (hESC) have ability to differentiate and provide neuronal or glial cells for transplantation (Erceg, Lainez, *et al.*; Keirstead, *et al.*; Lee, *et al.*) [10-12].

The present study evaluated the bowel/bladder control and sensation in the patient with SCI after hESC therapy.

Methods

Study Population: The patients diagnosed with SCI over a period of > 3 months were included in the study. The patients diagnosed with acute SCI or have received other forms of cell therapies within the last 12 months of the treatment and pregnant or lactating woman were excluded from the study.

All the patients had provided a written and video informed consent prior to start of the treatment. Independent physicians, and in house doctors and rehabilitation team scored the patients as per American Spinal Injury Association (ASIA) scale before and after the treatment. All these patients had undergone rehabilitation therapy before coming to our centre with no improvements.

Ethical statement

An independent ethics committee (IEC) approved the study protocol. The institutional committee for stem cell research and therapy (IC-SCRT) of Nutech Mediworld reported all the work related to embryonic stem cells to the National Apex Body and the Indian Council of Medical Research (ICMR).

Study Design

This was a retrospective analysis of bowel and bladder functions of 226 SCI patients treated with hESC therapy. The mean age of the patients was 28 years. The study was conducted from 24 May 2005 to 31 August 2012 at Nutech Mediworld, New Delhi, India.

The study consisted of four treatment phases (T1, T2, T3, T4) with gap phases (4-8 months) in between. During the treatment phases a dose of 0.25 ml (< 4 million cells) hESCs (cultured and maintained in-house in a xeno product free patented technology) were administered through intramuscular (i.m) route twice daily. Additionally, 1 ml hESCs (< 16 million cells) were administered every 10 days through intravenous (i.v) route and 1-5 ml hESCs were administered every 5-7 days by any of the supplemental routes. The subsequent treatment phases consisted a gap period of 4-8 months. Each treatment phase lasted 4 to 6 weeks. The patients with bowel and bladder

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problems were graded based on their symptoms. Detailed methodology has been described elsewhere (G Shroff and L Das; Shroff, Gupta and Barthakur) [13,14].

ASIA Impairment Scale

The patients were scored using ASIA (Steven C. Kirshblum) [15] grading scale viz. grade ‘A’- complete, ‘B’- sensory incomplete, ‘C’- motor incomplete, ‘D’- motor incomplete, ‘E’ - normal.

Bowel/Bladder sensation and control levels of Scoring

Five point of scoring was done for bowel/bladder sensation viz. level 1-no sensation of filling and voiding/evacuation, level 2-mild sensation of fullness but no feeling of voiding/evacuation, level 3-partial sensation of filling and voiding/evacuation, level 4-full sensation of filling and partial sensation of voiding/evacuation, level 5-reached normalcy.

Similarly, for bowel/bladder control, five levels of scoring was done viz. level 1- no control, level 2- control (≥ 1 min), level 3-control (≥ 5 min), level 4-control (≥ 10 min), level 5-reached normalcy.

Data Validation

The data was validated by Moody’s International (Document number NH-heSC-10-1), GVK Biosciences (NM-Hesc-10-1, 18 November 2010) and Quality of Austria Central Asia Pvt. Ltd. Accreditation Company (Document number QACA/OCT/2013/26).

Results

Patients

Of 226 patients, 200 (paraplegic-126, quadriplegic-74) and 204 (paraplegic-128, quadriplegic-76) subjects had SCI bowel and bladder sensation problems, respectively; while 203 (paraplegic-129, quadriplegic -74), and 209 (paraplegic-132, quadriplegic-77) subjects had bowel and bladder control problems, respectively.

Efficacy Evaluation

Bowel and bladder sensation of 200 subjects with affected bowel sensation, 163 subjects had no sensation of fullness and evacuation at the baseline. After hESC therapy, 135 (67.5%) subjects had mild, partial, or full sensation of bowel fullness, and 7 (3.5%) subjects reached normalcy. Similarly, of 204 subjects who had affected bladder sensation, 158 subjects had no sensation of fullness and evacuation at the baseline and after the treatment, 155 (76%) subjects had mild, partial, or full sensation of bladder fullness, while 7 (3.4%) subjects reached normalcy .

Level	Description	Bowel n (%)		Bladder n (%)	
		Admission	End of treatment	Admission	End of treatment
1	No sensation of fullness and evacuation	163 (81.5)	58 (29)	158 (77.5)	42 (20.6)
2	Mild sensation of fullness but no feeling of evacuation	22 (11)	80 (40)	31 (15.2)	79 (38.7)
3	Partial sensation of fullness and evacuation	8 (4)	36 (18)	9 (4.4)	49 (24)
4	Full sensation of fullness and partial sensation of evacuation	7 (3.5)	19 (9.5)	6 (2.9)	27 (13.2)
5	Above description 4, or reached normalcy	0	7 (3.5)	0	7 (3.4)

Table 1: Bowel and Bladder sensation in SCI patients after hESCs therapy.

At baseline, 148 (74%) subjects with bowel sensation problems had ASIA grade 'A'. After hESCs therapy, 128 (64%) subjects moved to higher grades 'B', 'C', 'D' and 'E'. Similarly, 150 (73.5%) subjects with bladder sensation problems had ASIA grade 'A' at the time of admission and after the therapy, 129 (63.2%) subjects moved to higher grade.

Baseline Characteristics		End of the Treatment				
		ASIA Scale, n (%)				
(N)	Grades	A	B	C	D	E
Bowel sensation (N = 200)	A (148)	38 (25.7)	47 (31.7)	63 (42.6)	0	0
	B (23)	0	9 (39.1)	13 (56.2)	0	1 (4.3)
	C (27)	0	0	24 (88.8)	3 (11.1)	0
	D (2)	0	0	0	1 (50)	1 (50)
Bladder sensation (N = 204)	A (150)	40 (26.7)	47 (31.3)	63 (42)	0	0
	B (24)	0	9 (37.5)	14 (58.3)	0	1 (4.2)
	C (28)	0	0	25 (89.3)	3 (10.7)	0
	D (2)	0	0	0	1 (50)	1(50)
Bowel Control (N = 203)	A (153)	41 (26.8)	49 (32)	63 (41.2)	0	0
	B (21)	0	6 (28.5)	14 (66.7)	0	1 (4.8)
	C (27)	0	0	24 (88.9)	3 (11.1)	0
	D (2)	0	0	0	1 (50)	1 (50)
Bladder Control (209)	A (153)	41 (26.8)	49 (32)	63 (41.2)	0	0
	B (24)	0	8 (33.3)	15 (62.5)	0	1 (4.2)
	C (30)	0	0	27 (90)	3 (10)	0
	D (2)	0	0	0	1 (50)	1 (50)

Table 2: Change in ASIA grades after hESCs therapy.

Bowel and bladder control

Of 203 subjects with affected bowel control, 189 subjects have no bowel control at the time of admission while none had normalcy. After the treatment, 95 (46.8%) subjects had bowel control, and four (2%) subjects reached normalcy. Similarly, of 209 subjects with affected bladder control, 193 subjects had no bladder control at the time of admission, while after the treatment, 113 (54%) subjects had bowel control, while four (1.9%) subjects reached normalcy.

At the time of admission, 153 (75.4%) subjects with bowel sensation problems and 153 (73.2%) subjects with bladder sensation problems had low ASIA score 'A'. After the therapy, 131 (64.5%) subjects (bowel sensation) and 132 (63.1%) subjects (bladder sensation) moved to higher ASIA grades.

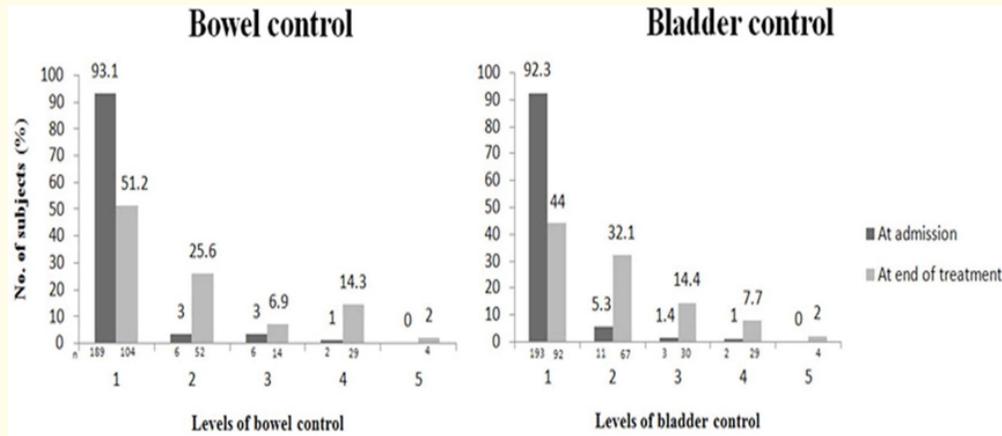


Figure 1: Bowel and Bladder control in SCI patients before and after hESCs treatment.

Discussion

Bowel and bladder dysfunction are associated with complications such as ulcers, ileus, reflux, pain, distention, impaction, chronic urinary tract infections, bladder cancer, renal failure, and hydronephrosis which can increase mortality risk (Benevento and Sipski; Gormley). Hence, more significant bowel/bladder dysfunction after SCI would foretell worse survival (Shavelle, *et al.*) [6]. Therefore, recovery of bladder function in SCI patients is regarded as one of the highest priorities (Anderson) [16]. The aim of this study was to explore the effects of hESCs on bowel and bladder function in patients with SCI. hESC therapy was effective in reducing Neurogenic bowel and bladder symptoms in SCI subjects. Majority of the subjects had mild, partial, or full sensation of bowel and bladder fullness after the hESCs therapy. The number of subjects with ASIA grade A were reduced from 74% to 19% (bowel sensation), 73.5% to 19.6% (bladder sensation), 75.4% to 20.2% (bowel control) and 73.2% to 19.6% (bladder control) after the therapy.

Bowel and bladder problems are the common complications in patients with SCI (McColl, *et al.*) [17]. A large number of patients with chronic SCI suffer fecal incontinence (Yasmeen, *et al.*) [7]. Glickman, *et al.* conducted a study to examine the workload and common problems facing primary care teams in SCI management. Of 139 subjects, 72% had urologic problems and 49.6% had bowel issues (Glickman S, Dalrymple-Hay M and GF) [18]. In a previous study by van Loo, *et al.* 72% of the enrolled patients with SCI, indicated the need for additional care of secondary conditions such as bladder and bowel regulation and pain (van Loo, *et al.*) [19]. In another study conducted by Warms, *et al.* to survey health care received by individuals with SCI and to describe desire of health care services, 80% of issues raised were related to disability. Of 59 subjects surveyed, 52.9% subjects discussed bladder or kidney problems, and 23% discussed bowel issues (Warms) [20]. In our study, 92.5% of SCI patients had bowel/bladder sensation and control problems initially.

Lower SCI is characterized by urinary incontinence, while upper SCI are characterized by bladder voiding difficulties (Sanchez Raya, *et al.*) [21]. To control the duration and frequency of the bowel program suppositories, laxatives and bulk-forming agents are used by a majority of patients (Yasmeen, *et al.*) [7]. However, there is a controversy regarding the best approach to be followed for the management of such patients (Sanchez Raya, *et al.*) [21]. Also, autonomic responses to the procedures of bladder filling and bowel emptying have been scarcely investigated (Faaborg, *et al.*) [22]. There is a need of safe, effective, and evidence-based bowel/bladder management strategies to be followed in patients with SCI (Francis).

The objective of treatment in SCI patients with Neurogenic bladder dysfunction is to ensure the functional preservation of the upper urinary tract with maximum continence and improved QoL (Sanchez Raya, *et al.*) [21]. Various pre clinical studies have shown that hESC-derived cells have potential to differentiate into mature Oligodendrocytes and neurons (Erceg, *et al.*; Kakinohana, *et al.*) [23,24].

We have also reported in our previous studies that treatment with hESCs were effective in treating neurodegenerative disorders (G. Shroff and L. Das; Shroff, Gupta and Barthakur) [13,14]. In the present study, hESCs were injected into the SCI patients having bowel/bladder sensation and control problems. We observed that after the therapy, bowel and bladder function improved in the patients, who were initially not able to control bowel and feel bladder fullness sensation. hESC transplantation in SCI is safe and effective and, improves clinical condition of patients as reported in our previous study (data communicated).

High level injuries and more severe ASIA impairment grade are more likely to lead to bowel and bladder dysfunction (Jeong, Cho and Oh) [25]. In the present study, majority of the subjects (N-153) had ASIA grade A with worse bowel/bladder sensation and control. However, after hESCs therapy, ASIA grade increased to higher levels "C", "D" and "E". Lima., *et al.* [26] in their study transplanted olfactory mucosa auto-grafts in 20 SCI patients with ASIA scale A. At the end of the treatment, ASIA grade improved from 'A' to 'C' in the six patients (Lima., *et al.*) [26]. In our study, the high grade of ASIA can be reflected in patients with improved bowel/bladder sensation and control.

David., *et al.* investigated the effects of toll like receptor (TLR9) antagonist on bladder function. They reported the beneficial effects of TLR9 antagonist on autonomic functions, as reflected by improved bladder voiding. They observed that TLR9 antagonist decreased SCI elicited urinary retention and ameliorates recovery of bladder function without affecting kidney function. TLR are the innate immunity receptors that are expressed in cells of both the immune and central nervous systems (David, Sampath., *et al.*) [27]. TLR have ability to reduce inflammatory response at injury epicenter after SCI that can in turn impact the function of the residual cells in the spared tissue and their communication with other cells, including those that convey information to and from the bladder (David, Ratnayake., *et al.* [28]; Kigerl., *et al.*) [29]. TLRs including TLR9 are also present on hESCs (Foldes., *et al.*) [30]. Thus, we can assume that hESCs may have modulated the innate immune receptor signaling in the spinal cord that can influence the effects of SCI leading to recovery of bladder function. However, the role of TLR9 in SCI is complex (Foldes., *et al.*) [30]. More studies are required to validate this concept.

Altogether, our results suggest that hESCs injection can clinically improve bowel and bladder function of SCI patients. There is a need for further studies of mechanisms responsible for the treatment of SCI patients with bowel/bladder sensation and control in response to hESCs therapy [31-36].

Conclusion

An improvement in bowel and bladder control, and bowel and bladder sensation was observed in SCI patients after hESCs therapy.

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