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Research Article

Mesenchymal Stem Cell Injection is Completely Safe, and Effective, for the Treatment of Chronic Back and Neck Pain: A Phase I Clinical Trial

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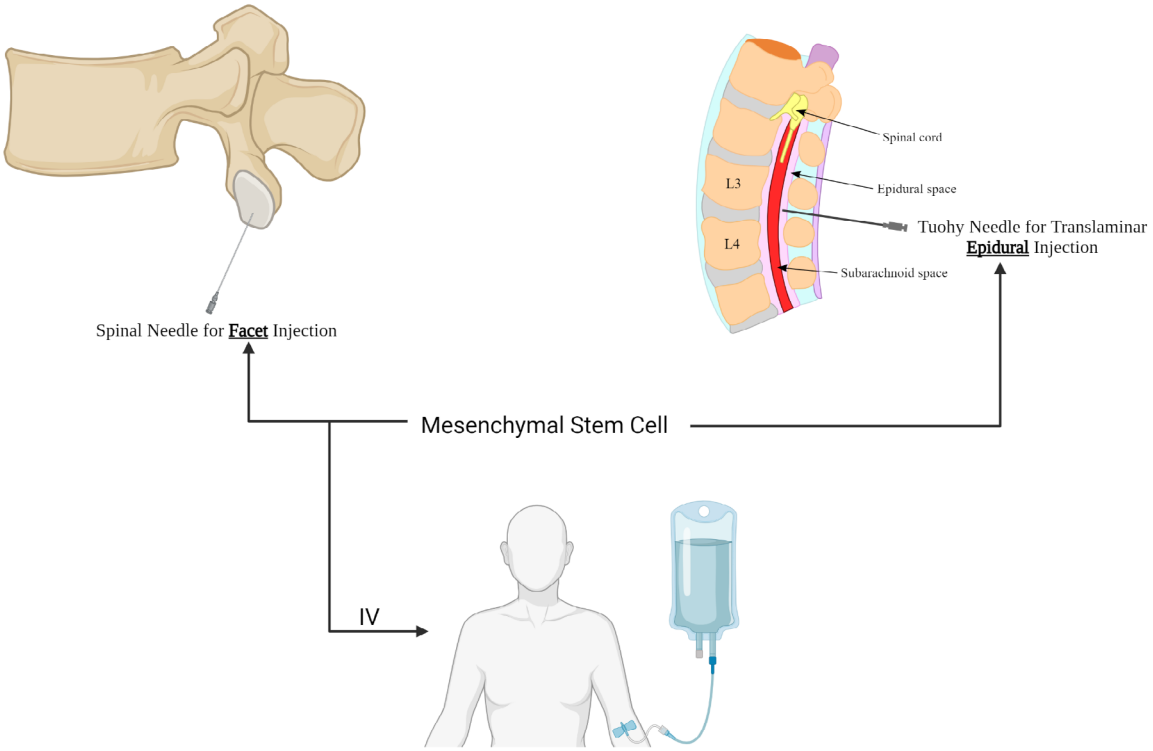
Abstract

Background: Recalcitrant chronic back and neck pain is an unsolved problem. Steroid injections are not significantly effective. Surgery is very painful, often fails, has high complication rates, and usually cannot be salvaged. Mesenchymal Stem Cells (MSCs) improve healing, are anti-inflammatory, and extremely safe. We hypothesized that MSC injection would be completely safe, and effective. **Methods:** Patients with chronic back and/or neck pain unresponsive to physical therapy were enrolled in a phase 1 trial. Safety was the primary endpoint, efficacy secondary. AlloRx (Vitro Biopharma, Golden Colorado) umbilical cord-derived MSCs were infused intravenously and injected translaminarly into the epidural space and facet joints. Patients were evaluated before and 1-, 3-, 6-, 12-, 18-, and 24-months post-treatment with VAS, Quebec score, and a global improvement rating. **Results:** 48 patients met inclusion criteria, with 36 having >6 months follow-up. >80% follow-up was obtained for all metrics at all time points. Patients typically recovered within five days. There were no serious adverse events. 67%, 74%, 61%, and 62% of patients showed clinically important pain relief at 1-, 3-, 6-, and 12-months post treatment. Nine patients had prior failed back surgery. Seven had follow-ups of >6 months. 88%, 86%, and 100% had significant pain relief at 3-, 6-, and 12-months after treatment. 88%, 86%, and 75% of neck pain patients had good pain relief at 3-, 6-, and 12-months. **Conclusions:** MSC epidural/facet/IV injection is completely safe, and also effective for back and neck pain.

Trial Registration: Federally registered institutional review board 00012420 approval was obtained for this study and informed consent was obtained for each patient.

Keywords: Stem Cells; Back Pain; Neck Pain

Abbreviations: MSC: Mesenchymal Stem Cell IV- Intravenously; VAS: Visual Analog Score; NSAID: Non-Steroidal Anti-Inflammatory Drug; HLA: Human Leukocyte Antigen; GI: Global Improvement; MRI: Magnetic Resonance Imaging; FDA: Food and Drug Administration; GMP: Good Manufacturing Practices; ISO: International Organization for Standardization; L: Lumbar; C: Cervical; HD: Herniated Disc; Inj.: Injection; MCID: Minimal Clinically Important Difference



Graphical Abstract: Loci of introduction of stem cells: facet joints, lumbar translaminar epidural space, and intravenous.

Introduction

Back (and neck) pain is the third most common reason, after skin and osteoarthritis/joint disorders, that patients of all ages see physicians in the United States [1]. The preferred initial treatment is physical therapy. However, if physical therapy fails, there is no safe effective backup treatment.

Medical treatment consists primarily of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [2,3]. However, NSAIDs only mask symptoms, have undesirable anti-healing properties and often have severe side effects [4,5]. Transforaminal epidural steroid injections are sometimes offered to patients; however, these injections are only effective for leg pain (sciatica), not back or neck pain [6-9]. Even for leg pain they only have short-term benefits, generally 3 months or less [10]. Rhizotomies (burning of the nerve) are used for facet related back pain but do not have proven efficacy [11]. Percutaneous disk shaving or burning is only indicated for leg pain with a herniated disk, not back pain [12].

The only other available potential solution is back surgery. Laminectomy and spinal fusion are the only spinal surgeries specifically designed to alleviate back pain. Spinal fusion surgery has been described as the second most painful surgery in existence [13]. It has a recovery time of at least 6 months, a relatively high failure rate, and a high incidence of often serious complications including infection, neurologic damage producing weakness, and chronic pain and numbness [14-16]. Additionally, studies have shown that when back surgery fails, repeat surgery is unlikely to produce a good result [17,18]. Laminectomy is not as painful as fusion but also has a relatively high failure and complication rate [19-21].

Mesenchymal Stem Cells (MSCs) are known to help damaged tissue heal and decrease pain [22-26]. Because they lack human leukocyte class II antigens (HLA), they do not engender rejection and can be injected into anyone without tissue matching [27,28]. Umbilical cord-derived MSCs have higher potency than older adult MSCs [29]. They have also been shown to be completely safe with a virtual absence of serious adverse events when properly used [22,26,30].

The anatomic site of origin of human back and neck pain is unclear [2, 31], even when MRIs are considered. Possible pain sources include the intervertebral disk space, the facet joints, or the surrounding ligamentous structures [31,32]. A few studies have injected MSCs or bone marrow aspirate concentrate into the intervertebral disk space with overall limited positive results [33,34].

However, these injections are painful, require sedation, generally take one or more months to fully recover from, and can be associated with infection or subsequent disk herniation [35].

We were not able to find any studies injecting the facet joints, although one paper injected next to them [36]. Stem cell papers also have virtually completely neglected the epidural space. Only one paper injected the epidural space at all and here only in a few patients without specifying results [37]. The epidural space however is appealing as a target because it allows for stem cells, which are genetically programmed to home to inflamed or damaged tissue, to freely seek out and migrate to inflamed areas anywhere in the back – including potentially diffusing into the intervertebral disk space through rents in the annulus fibrosis, as well as the facet joints [38,39]. While epidural injections are usually injected transforaminally, they can cause trauma to exiting nerve roots [40]. Epidural injections injected transforaminally also tend to constrain the flow of stem cells to some degree to the particular nerve root area injected. In contrast, translaminar injection allows free transport of the injected substance [41]. This can occur with a single injection. It generally takes under five minutes in the hands of a skilled practitioner under fluoroscopy and has a morbidity and complication rate near zero.

We felt that, when injected translaminarly into the epidural space, the homing properties of MSCs would allow them to seek out inflamed areas, including the disk space, without the treating physician needing to pierce the annulus fibrosus with a needle for an intervertebral disk injection [42-44]. We also felt that simultaneous intravenous MSC injection would be useful since cells will migrate into areas of inflammation. We previously noticed in our patients that IV injection alone tends to ameliorate back pain. In our experience intradiscal injections require sedation due to pain and at least one month, and usually several months, of recovery, whereas translaminar epidural and facet injections do not require sedation, and patients usually recover within one week.

Therefore, we hypothesized that MSC translaminar epidural and facet injection along with intravenous infusion, with or without disk injection, would be both effective and safe for patients with a primary complaint of back or neck pain, and that benefit would last longer than for steroid injections. We also felt that this regimen would produce significantly less procedural pain, avoid the need for sedation, and result in far faster recovery than if intervertebral disk spaces were injected. Since there is no other good treatment for chronic back and neck pain, we felt that the success of our method would be of potentially enormous benefit.

Methods

Inclusion Criteria

Inclusion criteria were chronic (more than one year) back or neck pain and failure of at least one course of physical therapy or supervised exercise. Patients could have sciatic or leg pain, but back or neck pain needed to be more severe than leg pain. In Table 1, patients were prospectively enrolled in this phase 1 clinical trial upon meeting the enrolment criteria and obtaining proper informed consent.

Variables	L Epidural	L Epidural + L Facet	L Epidural + C Facet	L Epidural + L Facet + C Facet	L Epidural + L Facet + Disk Inj	L Epidural + Disk Inj
Number	4	22	5	5	11	1
Age						
<34		2			1	
35-54		3	2	1	4	
>55	4	17	3	4	6	1
Sex						
Male	3	16	4	2	9	1
Female	1	6	1	3	2	
BMI						
18.5-24.9	1	9	1	3	2	
25.0-29.9	2	8	3	1	8	1
>30	1	5	1	1	1	

Table 1: Patient Demographic and Treatment Information.

Ratings

Patients were evaluated using a Quebec rating scale, an estimate of post-treatment Global Improvement (GI), and a visual analogue score (VAS) estimate of pain severity. Evaluation was carried out within one month prior to treatment and then at 1-, 3-, 6-, 12-, 18-, and 24-months after treatment. All patients had an MRI scan before treatment.

Clinically Significant Improvement

Clinically significant improvement was considered to be present if a patient had a reduction in VAS of 2 or more points, global improvement of 30% or more, or Quebec rating improvement of at least 15 points at a given time point.

Medications

All patients had discontinuance of all non-steroidal anti-inflammatory drugs, corticosteroids, and opiates before and after treatment. Anti-coagulants were also discontinued before injection and re-started the day after injection.

MSC Injection Technique

The MSC injections were performed under local anaesthetic in an operating room using sterile technique with fluoroscopic guidance by author KC, a highly experienced board-certified anaesthesiologist and pain specialist. Sedation was used only in patients in whom disk injections were also performed.

Injection Protocol

In patients with low back pain the facets of L2-5 were injected bilaterally. In patients with neck pain, the facets of C3-6 were injected bilaterally. Each facet was injected with between 1.5 to 3 million cells. Each patient also had an injection of 20 to 25 million cells into the epidural space using a translaminar approach regardless of whether the patient had lumbar pain, cervical pain, or both. Patients were told that intervertebral disk injection might be a second recommended procedure at a later date if the initial epidural/facet injection failed. Given these instructions, twelve patients requested to have the intervertebral disk space injected at the time of the initial injection with 25 million cells per intervertebral disk space into 2 intervertebral disk spaces. Patients also received at least 100 million stem cells intravenously in a dose of approximately 1 million cells per kg of body weight.

Cells Used

All patients were treated with umbilical cord-derived mesenchymal stem cells from Vitro Biopharma (https://www.vitrobiopharma.com/) in Golden Colorado. Vitro Biopharma is an FDA-registered biomanufacturing firm whose cells have been FDA-authorized for use in human patients. They use GMP technique. They also have international ISO 9001 and 13485 certifications.

Post-Treatment Protocol

Patients were advised to limit activities according to pain. They were allowed to begin exercise as early as 3 days after treatment if they had no pain while doing so. Pain after treatment was controlled with ice, usually from a motorized ice machine, and acetaminophen (Tylenol) as needed. Some patients needed a few doses of Tramadol. A few of the patients with disk injections, but none of the patients with only epidural and facet injections, needed two or three doses of hydrocodone. NSAIDs, aspirin, and anticoagulants were prohibited before treatment to avoid bleeding into the spine and surrounding tissues. Corticosteroids were prohibited before treatment to avoid interfering with the effects of the stem cells.

Results

Follow-Up/MCID/Duration of Effect

For all patients, and various patient subgroups below, there are listed for each time point: percent follow-up achieved, percent of patients who achieved MCID (efficacy), seen in Table 2, and how long that improvement lasted (duration), which can be seen in Table 3.

	Months Post Treatment		
	3M	6M	12M
All Patients	29/39 = 74%	22/36 = 61%	18/29 = 62%
Patients Divided into Treatment Groups			
L Epidural + Facet	16/24 = 67%	14/23 = 61%	11/18 = 61%
L Epidural + Facet* + Disk Inj	10/11 = 91%	6/9 = 67%	5/7 = 71%
C Facet + L Epidural	7/8 = 88%	6/7 = 86%	3/4 = 75%
Patients Divided into Diagnostic Categories			
HD	15/18 = 83%	11/16 = 69%	11/13 = 85%
Pre-VAS≥8	15/17 = 88%	11/15 = 73%	8/13 = 62%
Previous Failed Back Surgery	7/8 = 88%	6/7 = 86%	6/6 = 100%
Spondylolisthesis	9/13 = 69%	8/13 = 62%	7/11 = 64%

Legend: M: Months, L: Lumbar; C: Cervical; HD: Herniated disk; Inj: Injection; VAS: Visual Analogue Scale; GI: Global Improvement.

Table 2: Percent of Patients with Clinically Significant Improvement.

	Pre-Treatment	**3M**	**6M**	**12M**	**18M**
		% Initial Responders	Continued Response in Responders		
All Patients	-	74% (29/39)	85% (22/26)	82% (18/22)	60% (6/10)
VAS	7.1	3.2	3.1	2.9	2.9
GI	N/A	63%	67%	66%	56%
Quebec	33	16	16	11	8
L Epidural + Facet	-	67% (16/24)	93% (14/15)	92% (14/15)	100% (3/3)
VAS	7.2	3.3	3.6	2.9	0.3
GI	N/A	72%	70%	69%	91%
Quebec	34	17	18	14	0
L Epidural + Facet + Disk Inj	-	91% (10/11)	75% (6/8)	71% (5/7)	40% (2/5)
VAS	6.8	3.3	2.5	3	4
GI	N/A	48%	61%	61%	38%
Quebec	29	13	12	6	8
C Facet + L Epidural	-	88% (7/8)	100% (6/6)	100% (3/3)	100% (1/1)
VAS	6.3	2.7	2.6	1.8	0
GI	N/A	75%	72%	78%	100%
Quebec	24	11	17	5	0
HD	-	83% (15/18)	85% (11/13)	92% (11/12)	67% (2/3)

VAS	6.7	2.5	2.8	2.5	2
GI	N/A	68%	68%	71%	58%
Quebec	29	17	14	11	0
Pre-VAS≥8	-	88% (15/17)	85% (11/13)	73% (8/11)	50% (2/4)
VAS	8.3	3.7	3.6	3.2	4
GI	N/A	56%	63%	59%	49%
Quebec	40	22	20	18	13
Previous Failed Back Surgery	-	88% (7/8)	100% (6/6)	100% (6/6)	100% (3/3)
VAS	7.6	4.1	2.2	1	0
GI	N/A	43%	79%	85%	98%
Quebec	44	30	25	22	20
Spondylolisthesis	-	69% (9/13)	89% (8/9)	88% (7/8)	100% (1/1)
VAS	7.8	2.4	2.8	2.4	0
GI	N/A	77%	74%	70%	99%
Quebec	42	23	18	18	0
Legend: M: Months, L: Lumbar; C: Cervical; HD: Herniated disk; Inj: Injection; VAS: Visual Analogue Scale; GI: Global Improvement.					

Table 3: Duration of Improvement Among Those Initially Responding to Treatment.

All Patients: Lumbar Epidural/ Lumbar or Cervical Facet with Or Without Disk Injections

Follow-Up: For all study patients meeting inclusion criteria, follow-up was available at 1-, 3-, 6-, 12-, and 18-months for 96% (46/48), 81% (39/48), 75% (36/48), 60% (29/48), and 33% (16/48) of patients.

Efficacy: At 1-, 3-, 6-, and 12-months post-treatment, MCID was seen in 67% (31/46), 74% (29/39), 61% (22/36), and 62% (18/29) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 85% (22/26), 82% (18/22), and 60% (6/10) of treatment responders at 6-, 12-, and 18-months respectively.

Lumbar Epidural/Lumbar and/or Cervical Facet Without Disk Injections

Follow-Up: Twenty-nine patients received epidural and facet injections without disk injection. Follow-up was available at 3-, 6-, and 12-months for 83% (24/29), 79% (23/29), and 62% (18/29) of patients.

Efficacy: At 3-, 6-, and 12-months post-treatment, MCID was seen in 67% (16/24), 61% (14/23), and 61% (11/18) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 93% (14/15), 92% (11/12), and 100% (3/3) of treatment responders at 6-, 12-, and 18-months respectively.

Lumbar Epidural/Lumbar Facet with Disk Injection

Follow-Up: Twelve patients had disk injections in addition to facet and epidural injections (one patient had an epidural injection without facet injections). Follow-up was available at 3-, 6-, and 12-months for 100% (11/11), 82% (9/11), and 64% (7/11) of patients.

Efficacy: At 3-, 6-, and 12-months post-treatment, MCID was seen in 91% (10/11), 67% (6/9), and 71% (5/7) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 75% (6/8), 71% (5/7), and 40% (2/5) of treatment responders at 6-, 12-, and 18-months respectively.

Lumbar Epidural/Cervical Facet Injections

Follow-Up: Ten patients received lumbar epidural and cervical facet injections. Follow-up was available at 3-, 6-, and 12-months for 80% (8/10), 70% (7/10), and 40% (4/10) of patients.

Efficacy: At 3-, 6-, and 12-months post-treatment, MCID was seen in 88% (7/8), 86% (6/7), and 75% (3/4) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 100% (6/6), 100% (3/3), and 100% (1/1) of treatment responders at 6-, 12-, and 18-months respectively.

Patients with Disk Herniation

Follow-Up: Twenty-one patients had a diagnosis of HD (herniated disk). Follow-up was available at 3-, 6-, and 12-months for 86% (18/21), 76% (16/21), and 62% (13/21) of patients.

Efficacy: At 3-, 6-, and 12-months post-treatment, MCID was seen in 83% (15/18), 69% (11/16), and 85% (11/13) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 85% (11/13), 92% (11/12), and 67% (2/3) of treatment responders at 6-, 12-, and 18-months respectively.

Patients with VAS Scores of 8 or Greater Pre-Treatment

Follow-Up: Eighteen patients had a pre-treatment VAS score of 8 or greater. Follow-up was available at 3-, 6-, and 12-months for 94% (17/18), 83% (15/18), and 72% (13/18).

Efficacy: At 3-, 6-, and 12-months, MCID was seen in 88% (15/17), 73% (11/15), and 62% (8/13) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 85% (11/13), 73% (8/11), and 50% (2/4) of treatment responders at 6-, 12-, and 18-months respectively.

Patients with Failed Back/Neck Surgery

Follow-Up: Nine patients had failed prior back surgery, seven of whom had follow-up of 6 months or greater. Follow-up was available at 3-, 6-, and 12-months for 89% (8/9), 78% (7/9), and 67% (6/9) of patients respectively.

Efficacy: At 3-, 6-, and 12-months MCID was seen in 88% (7/8), 86% (6/7), and 86% (6/7) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 100% (6/6), 100% (6/6), and 100% (3/3) of treatment responders at 6-, 12-, and 18-months respectively.

Patients with Spondylolisthesis

Follow-Up: Thirteen patients had a diagnosis of spondylolisthesis confirmed by MRI. Follow-up was available at 3-, 6-, and 12-months for 100% (13/13), 100% (13/13), and 85% (11/13) of patients respectively.

Efficacy: At 3-, 6-, and 12-months MCID was seen in 69% (9/13), 62% (8/13), and 64% (7/11) of patients respectively.

Duration of Improvement: Continued clinically significant improvement was observed in 89% (8/9), 88% (7/8), and 100% (1/1) of treatment responders at 6-, 12-, and 18-months respectively.

Mean Magnitude of Improvement in Responders

Table 4 analyzes the mean magnitude of improvement in responders of treatment by evaluating the VAS, Global Improvement, and Quebec scores at 1 month, 3 months, 6 months, 12 months, and 18 months.

		Months Post Treatment				
	Pre-Treatment	1M	3M	6M	12M	18M
VAS	6.7	4.1	4	4	3.6	3.3
Quebec	32	21	21	21	18	13
GI	N/A	43%	47%	48%	50%	38%
Legend: M: Months, VAS: Visual Analogue Scale; GI: Global Improvement						

Table 4: Mean Improvement of All Patients.

VAS: Pre-treatment: 7.1; Post-treatment: 3.2, 3.1, 2.9, and 2.9 at 3-, 6-, 12- and 18-months respectively.

Global Improvement: 63%, 67%, 66%, and 56% at 3-, 6-, 12-, and 18-months respectively.

Quebec: Pre-treatment: 33; Post-treatment: 16, 16, 11, and 8 at 3-, 6-, 12-, and 18-months respectively.

Post-Treatment Parameters

Time to Recovery: Most patients who had facet and epidural injections recovered within 1 week and had often already significantly improved. Patients who had disk injections recovered much more slowly and were usually not back to baseline until 1-2 months post-injection with further improvement following.

Survivorship Without Subsequent Back Surgery: 3 of 31 patients, 10%, elected surgery subsequent to stem cell injection: a survivorship without surgery of 90%. Two of the three patients who elected to have surgery were significantly improved after stem cell treatment but elected surgery to allow even greater function for vigorous activities without pain.

Repeat Back Injections: Two patients had significant improvement after their initial epidural injection but elected a second injection in an attempt to further improve their result.

Patient 1: The first patient had an epidural and lumbar facet injection initially. For his second injection, we repeated the

epidural and facet joint injection and injected two lumbar disks in addition. The second injections completely eliminated his residual pain.

Patient 2: The second patient had only an epidural injection initially. For his second injection, we repeated the epidural and also injected his lumbar facets and two lumbar disks. The second injections completely eliminated his residual pain.

Repeat Intravenous Infusions: One patient had good success from epidural/facet injection and intravenous infusion but had some residual pain. She elected to repeat only the IV infusion. This resulted in further significant pain reduction, although still not complete improvement.

Complications and Serious Adverse Events

There were no complications or serious adverse events in any patient.

Discussion

This study shows, for the first time, that MSC translaminar epidural and facet injection with IV infusion, without disk injection, is rapidly effective and enduring in relieving chronic back and/or neck pain in most patients. MSC treatment had an efficacy rate similar to surgery in relieving pain, but unlike surgery, there was a complete absence of serious adverse events or complications. And whereas spine surgery is quite painful and requires 6 months of recovery most MSC patients were fully recovered and already improved 1 week after treatment.

The Role for Disk Space Injections: Adding lumbar disk space injection to the epidural/facet/IV regimen did not significantly improve results. However, two patients with partial relief after epidural and facet injections alone had further relief from a second injection of epidural/facet/IV but with concomitant disk injection. We therefore now reserve disk space injections for patients desiring further treatment after their initial epidural/facet/IV treatment but do not offer it as initial treatment. We feel that the avoidance of morbidity, risk, and required sedation of disk space injections is a significant advantage of our primary epidural/facet/IV without disk space injection protocol.

Patient Subgroup Results

Below are listed several subgroups that might have been expected to have compromised results, but who in fact had equivalent or better efficacy in relieving back or neck pain than the overall group.

Good Results for More Severe Pain: Patients with a VAS score of 8 or more, i.e. the highest levels of pain, actually had similar results to those with lower levels of pain after stem cell treatment, 73% and 62% at six months and 1-year MCID. This differs from back surgery where those with more severe pain tend to have worse outcomes [45].

Good Results for Back Pain in Herniated Disk Patients: The success rate for back pain relief for patients with herniated disks was among the highest of all patients: 69% at 6 months and 85% at one year.

Good Results with Spondylolisthesis: This is an advanced degenerative change but did not result in worse outcomes than the overall group with 64% efficacy at one year.

Good Results After Failed Back Surgery: Nine patients in this series had failed prior back surgery. Six of the seven patients who had follow-up out to 12 months had significant and enduring improvement after stem cell treatment. Although a small sample size, this is the only effective treatment for failed back surgery thus far reported. It contrasts sharply with repeat back surgery where a second operation is helpful in only a minority of patients [17]. The possibility that stem cell treatment could be a reliable salvage for failed back surgery syndrome is very significant since failed back surgery patients are the likeliest to be drug addicted and have severe unremitting pain, and there is no other consistently effective treatment.

Good Results for Neck Pain: Our neck patients had a one-year success rate of 75% which is greater than the overall group rate of 62%. We found that the epidural injection that is used for low back pain - administered in the lumbar (lower) spine - is equally effective for neck pain. This is a truly remarkable finding first reported by our center [46]. We discovered that stem cells, which are programmed to seek out inflamed tissue, will migrate from the lower spine to the neck in the epidural space if there is inflammation and pain in the neck. This is important because a lumbar translaminar injection is easy to administer and very safe, whereas a cervical epidural injection is more difficult and has some risk [47]. Happily, the homing properties of stem cells mean that the epidurals injected for neck pain, as well as for low back pain, can all be done easily and safely in the lower back.

Excellent Survivorship Without Surgery After Stem Cell Treatment: Only three patients out of the more than 31 treated with stem cell injection with one-year follow-up elected to have subsequent back surgery. Two of them had significant improvement from stem cell treatment but wanted even greater improvement. The net result is that back surgery was avoided in 90% of patients. Given the pain, complication rate, and expense of back surgery this is a very important benefit of stem cell treatment.

MSC Injection Results Compared to Other Treatments

Back/Neck Surgery

Equal Efficacy: Pain relief at one year is roughly the same for MSC injection and back surgery.

Little Pain After MSC Injection: Stem cell injection produces minimal discomfort, whereas spine fusion has been found to be the second most painful of all surgical procedures.

Rapid Time to Improvement After MSC Injection: Stem cell patients generally feel better within 5 days of their stem cell treatment, whereas for back surgery, and especially fusion, patients take many months to a year before they are fully recovered.

No Complications/Serious Adverse Events: Spinal laminectomy/fusion patients have an estimated 27.1% rate of complications [21]. One series found dural tears in 15.7%, excessive blood loss in 5.7%, and facet joint dysfunction leading to facet joint removal in 2.9% of patients. Laminectomy patients alone have a 10% reoperation rate and when combined with fusion they have a roughly 20% re-operation rate [19]. Spinal fusion patients have an estimated 18% rate of complications [48]. MSC injection patients had no complications or serious adverse events of any kind.

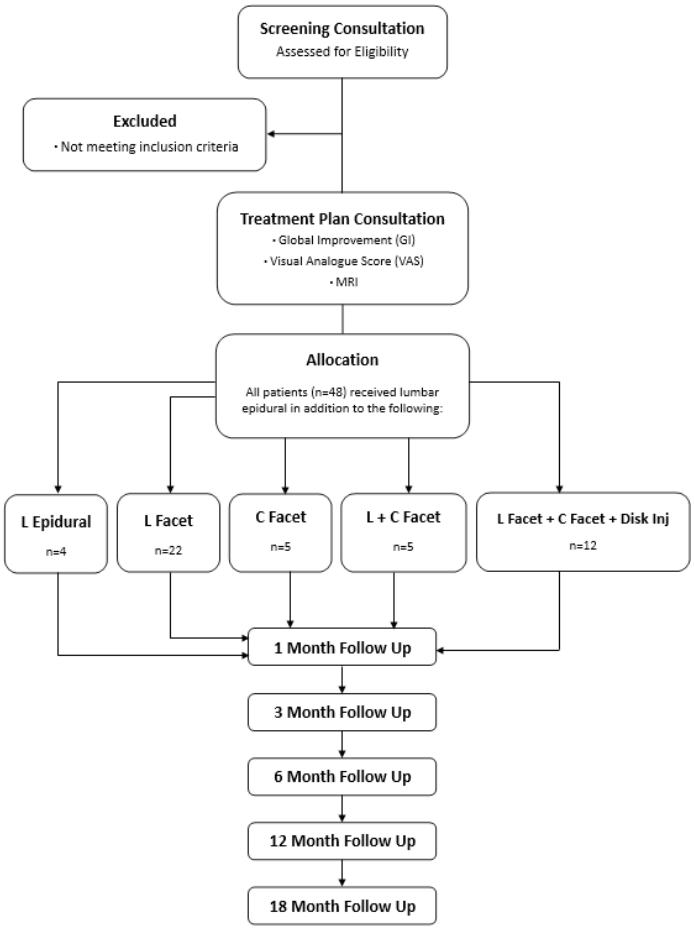
Lower Cost: Stem cell treatment is far less expensive to perform than back surgery and less expensive because there are no painful complications to treat.

Less Medication: Whereas back surgery patients frequently take pain, anti-inflammatory and muscle-relaxing medications, successful stem cell patients do not need medications of any kind.

Corticosteroid Injections: Steroid injections are indicated for radicular pain but are not generally indicated or effective for back or neck pain [49,50]. Their efficacy is usually only a few months [51]. Repeatability is limited by the side effects of repetitive steroid use. MSC treatment in contrast generally lasts at least one year, is specifically effective for back and neck pain, and can be repeated as often as needed.

Study Strengths and Weaknesses

Strengths are the relatively large number of patients with over 80% follow-up for all rating instruments at all time points. Another strength is the length of follow-up of over a year. Most injection studies only provide data for up to three or six months. The lack of a control group is a weakness but unnecessary in this group of chronic patients. Controls would consist of therapy and medications and all patients had failed this regimen. Sham procedure controls are impossible and probably unethical. We believe the therapeutic effect seen is clearly the result of the treatment provided [52].



Flow chart

Conclusions

Mesenchymal stem cell translaminar epidural and facet injections with IV infusion is completely safe in back and neck pain patients. It also rapidly and prolongedly alleviated pain in most patients and was effective after failed back surgery in a high percentage of patients.

Declarations

Funding

The study was patient-funded.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

Title of Approved Project: Safety of Cultured Allogeneic Adult Umbilical Cord Derived Mesenchymal Stem Cells for the Treatment of Osteoarthritis

Name of the Institutional Approval Committee or Unit: The Foundation for Regenerative Medicine and Orthopaedics' IRB

Approval Number: 202127UC

Date of Ethics Approval: December 1st, 2022

The study was approved by an ethics committee before beginning. All subjects signed a consent form stating that they were aware of the risks and benefits of the procedures and that they consented to take part in the research study.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

MH, KJ, EC, RD, and AA all performed data acquisition, data analysis, literature search, and literature analysis.

CP performed patient clinical evaluation and follow-up. He also performed data analysis, study conception, study design, and created the prose for this paper. KC performed patient clinical evaluation, patient procedures, and contributed to the study design.

References

1. St Sauver JL, Warner DO, Yawn BP, Jacobson DJ, McGree ME, et al. (2013) Why patients visit their doctors: assessing the most prevalent conditions in a defined American population. Mayo Clin Proc 88: 56-67.
2. Casiano VE, Sarwan G, Dydyk AM, Varacallo M (2023) Back Pain. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
3. van der Gaag WH, Roelofs PD, Enthoven WT, van Tulder MW, Koes BW (2020) Non-steroidal anti-inflammatory drugs for acute low back pain. Cochrane Database Syst Rev 4: CD013581.
4. Bindu S, Mazumder S, Bandyopadhyay U (2020) Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol 180: 114147.
5. French EJ, Go MF (2009) Treatment and chemoprevention of NSAID-associated gastrointestinal complications. Ther Clin Risk Manag 5: 65-73.
6. Candido KD, Knezevic N (2013) Cervical epidural steroid injections for the treatment of cervical spinal (neck) pain. Curr Pain Headache Rep 17: 314.
7. Carassiti M, Pascarella G, Strumia A, Russo F, Papalia GF, et al. (2021) Epidural Steroid Injections for Low Back Pain: A Narrative Review. Int J Environ Res Public Health 19: 231.
8. Friedly JL, Comstock BA, Turner JA, Heagerty PJ, Deyo RA, et al. (2014) A randomized trial of epidural glucocorticoid injections for spinal stenosis. N Engl J Med 371: 11-21.
9. Manchikanti L, Knezevic E, Knezevic NN, Sanapati MR, Thota S, et al. (2021) Epidural Injections for Lumbar Radiculopathy or Sciatica: A Comparative Systematic Review and Meta-Analysis of Cochrane Review. Pain Physician 24: E539-E554.
10. Oliveira CB, Maher CG, Ferreira ML, Hancock MJ, Oliveira VC, et al. (2020) Epidural corticosteroid injections for lumbosacral radicular pain. Cochrane Database Syst Rev 4: CD013577.
11. Yeung SST, Visintini S (2018) Percutaneous Rhizotomy for Chronic Back or Neck Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health.
12. Singh V, Derby R (2006) Percutaneous lumbar disc decompression. Pain Physician 9: 139-146.
13. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, et al. (2013) Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology 118: 934-944.
14. Fritzell P, Hägg O, Nordwall A; Swedish Lumbar Spine Study Group (2003) Complications in lumbar fusion surgery for chronic low back pain: comparison of three surgical techniques used in a prospective randomized study. A report from the Swedish Lumbar Spine Study Group. Eur Spine J 12: 178-189.
15. Papadakis M, Aggeliki L, Papadopoulos EC, Girardi FP (2013) Common surgical complications in degenerative spinal surgery. World J Orthop 4: 62-66.
16. Proietti L, Scaramuzzo L, Schiro' GR, Sessa S, Logroscino CA (2013) Complications in lumbar spine surgery: A retrospective analysis. Indian J Orthop 47: 340-345.
17. Daniell JR, Osti OL (2018) Failed Back Surgery Syndrome: A Review Article. Asian Spine J 12: 372-379.
18. Nachemson AL (1993) Evaluation of results in lumbar spine surgery. Acta Orthop Scand Suppl 251: 130-133.
19. Epstein NE (2018) Lower complication and reoperation rates for laminectomy rather than MI TLIF/other fusions for degenerative lumbar disease/spondylolisthesis: A review. Surg Neurol Int 9: 55.
20. Katz JN, Lipson SJ, Larson MG, McInnes JM, Fossel AH, et al. (1991) The outcome of decompressive laminectomy for degenerative lumbar stenosis. J Bone Joint Surg Am 73: 809-816.
21. Williams MG, Wafai AM, Podmore MD (2017) Functional outcomes of laminectomy and laminotomy for the surgical management lumbar spine stenosis. J Spine Surg 3: 580-586.
22. Barmada A, Sharan J, Band N, Rumschlag T, Yaqub A, et al. (2023) Review of the Published Literature Confirms the Safety of Intravenous Infusion of Mesenchymal Stem Cells. Curr Stem Cell Res Ther 18: 779-786.
23. Maxson S, Lopez EA, Yoo D, Danilkovitch-Miagkova A, Leroux MA (2012) Concise review: role of mesenchymal stem cells in wound repair. Stem Cells Transl Med 1: 142-149.
24. Nagamura-Inoue T, He H (2014) Umbilical cord-derived mesenchymal stem cells: Their advantages and potential clinical utility. World J Stem Cells 6: 195-202.
25. Padda J, Khalid K, Zubair U, Al Hennawi H, Yadav J, et al. (2021) Stem Cell Therapy and Its Significance in Pain Management. Cureus 13: e17258.

26. Yubo M, Yanyan L, Li L, Tao S, Bo L, et al. (2017) Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: A meta-analysis. PLoS One 12: e0175449.

27. Klyushnenkova E, Mosca JD, Zernetkina V, Majumdar MK, Beggs KJ, et al. (2005) T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. J Biomed Sci 12: 47-57.

28. Le Blanc K, Tammik C, Rosendahl K, Zetterberg E, Ringdén (2003) HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol 31: 890-896.

29. Tonrey T, Musick J, Dean R, Patel K (2020) Comparative Analysis of Adult Mesenchymal Stem Cells Derived from Adipose, Bone-Marrow, Placenta, and Umbilical Cord Tissue. Vitro Biopharma.

30. Wang Y, Han ZB, Song YP, Han ZC (2012) Safety of mesenchymal stem cells for clinical application. Stem Cells Int 2012: 652034.

31. Knezevic NN, Candido KD, Vlaeyen JWS, Van Zundert J, Cohen SP (2021) Low back pain. Lancet 398: 78-92.

32. Urits I, Burshtein A, Sharma M, Testa L, Gold PA, et al. (2091) Low Back Pain, a Comprehensive Review: Pathophysiology, Diagnosis, and Treatment. Curr Pain Headache Rep 23: 23.

33. Elabd C, Centeno CJ, Schultz JR, Lutz G, Ichim T, et al. (2016) Intradiscal injection of autologous, hypoxic cultured bone marrow-derived mesenchymal stem cells in five patients with chronic lower back pain: a long-term safety and feasibility study. J Transl Med 14: 253.

34. Papadimitriou N, Hebelka H, Hingert D, Baranto A, Barreto Henriksson H, et al. (2021) Intradiscal Injection of Iron-Labeled Autologous Mesenchymal Stromal Cells in Patients With Chronic Low Back Pain: A Feasibility Study With 2 Years Follow-Up. Int J Spine Surg 15: 1201-1209.

35. Jerome MA, Lutz C, Lutz GE (2021) Risks of Intradiscal Orthobiologic Injections: A Review of the Literature and Case Series Presentation. Int J Spine Surg 15: 26-39.

36. Rothoerl R, Tomelden J, Alt EU (2023) Safety and Efficacy of Autologous Stem Cell Treatment for Facetogenic Chronic Back Pain. J Pers Med 13: 436.

37. Atluri S, Murphy MB, Dragella R, Herrera J, Boachie-Adjei K, et al. (2022) Evaluation of the Effectiveness of Autologous Bone Marrow Mesenchymal Stem Cells in the Treatment of Chronic Low Back Pain Due to Severe Lumbar Spinal Degeneration: A 12-Month, Open-Label, Prospective Controlled Trial. Pain Physician 25: 193-207.

38. Marino L, Castaldi MA, Rosamilio R, Ragni E, Vitolo R, et al. (2019) Mesenchymal Stem Cells from the Wharton's Jelly of the Human Umbilical Cord: Biological Properties and Therapeutic Potential. Int J Stem Cells 12: 218-226.

39. Tenny S, Gillis CC (2023) Annular Disc Tear. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

40. Chang A, Ng AT (2020) Complications Associated with Lumbar Transforaminal Epidural Steroid Injections. Curr Pain Headache Rep 24: 67.

41. Landa J, Kim Y (2012) Outcomes of interlaminar and transforminal spinal injections. Bull NYU Hosp Jt Dis 70: 6-10.

42. De Becker A, Riet IV (2016) Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy? World J Stem Cells 8: 73-87.

43. Rustad KC, Gurtner GC (2012) Mesenchymal Stem Cells Home to Sites of Injury and Inflammation. Adv Wound Care (New Rochelle) 1: 147-152.

44. Sordi V (2009) Mesenchymal stem cell homing capacity. Transplantation 87: S42-S45.

45. Voorhies RM, Jiang X, Thomas N (2007) Predicting outcome in the surgical treatment of lumbar radiculopathy using the Pain Drawing Score, McGill Short Form Pain Questionnaire, and risk factors including psychosocial issues and axial joint pain. Spine J 7: 516-524.

46. Sharan J, Barmada A, Prodromos C, Candido K (2023) First Human Report of Relief of Lumbar and Cervical Discogenic and Arthritic Back Pain after Epidural and Facet Joint Mesenchymal Stem Cell Injection: A Case Report. Curr Stem Cell Res Ther 18: 1013-1015.

47. Trentman TL, Rosenfeld DM, Seamans DP, Hentz JG, Stanek JP (2009) Vasovagal reactions and other complications of cervical vs. lumbar translaminar epidural steroid injections. Pain Pract 9: 59-64.

48. Brox JI, Sørensen R, Friis A, Nygaard Ø, Indahl A, et al. (2003) Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine (Phila Pa 1976) 28: 1913-1921.

49. Benzon HT (1986) Epidural steroid injections for low back pain and lumbosacral radiculopathy. Pain 24: 277-295.

50. Patel K, Chopra P, Upadhyayula S (2023) Epidural Steroid Injections. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

51. Curatolo M, Rundell SD, Gold LS, Suri P, Friedly JL, et al. (2022) Long-term effectiveness of epidural steroid injections after new episodes of low back pain in older adults. Eur J Pain 26: 1469-1480.

52. Bydon M, Macki M, Abt NB, Sciubba DM, Wolinsky JP, et al. (2015) Clinical and surgical outcomes after lumbar laminectomy: An analysis of 500 patients. Surg Neurol Int 6: S190-S193.