Published in final edited form as:

Spine (Phila Pa 1976). 2008 August 15; 33(18): E624–E629. doi:10.1097/BRS.0b013e3181822711.

A randomized placebo-controlled trial of single-dose IM corticosteroid for radicular low back pain

BW Friedman, MD, D Esses, MD, C Solorzano, RPh, HK Choi, MD, M Cole, MD, M Davitt, MD, PE Bijur, PhD, and E.J Gallagher, MD

Abstract

Study Design—A randomized, double-blind, placebo-controlled, clinical trial of patients with radicular low back pain who present to an emergency department (ED) within one week of pain onset. Objective: We hypothesized that a single intramuscular 160mg dose of methylprednisolone acetate would improve pain and functional outcomes one month after ED discharge if the corticosteroid were administered early in disease symptomatology.

Summary of Background data—Parenteral corticosteroids are not recommended for acute, radicular low back pain, though their role in this disease process is ill-defined. To date, this medication class has only been studied in a highly selected group of patients requiring hospitalization.

Methods—Adults between the ages of 21 and 50 who presented to an ED with low back pain and a positive straight leg raise test were enrolled. The primary outcome was change in pain intensity on an 11 point numerical rating scale one month after ED visit. Secondary outcomes one month after ED discharge included analgesic use, functional disability and adverse medication effects

Results—637 patients were approached for participation, 133 were eligible, and 82 were randomized. Baseline characteristics were comparable between the groups. The primary outcome, a comparison of the mean improvement in pain intensity, favored methylprednisolone by 1.3 ($p=0.10$). Some secondary outcomes favored methylprednisolone, such as use of analgesic medication within the previous 24 hours (22% vs. 43%, 95%CI for difference of 20%: 0, 40%) and functional disability (19% vs. 49%, 95%CI for difference of 29%: 9, 49%). Adverse medication effects one week after ED discharge were reported by 32% of methylprednisolone and 24% of placebo patients (95%CI for difference of 9%: -12%, 30%).

Conclusions—This study was a negative study, though there was a suggestion of benefit of methylprednisolone acetate in a population of young adults with acute radicular low back pain. Further work with a larger sample of patients is needed.

Keywords

emergency department; radicular low back pain; corticosteroids; methylprednisolone

Corresponding author and address for reprints: Benjamin W. Friedman, MD, Department of Emergency Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, 111 East 210th Street, Bronx, New York 10467, Email: E-mail: befriedm@montefiore.org, Phone: (718) 920-6626, Fax: (718) 798-0730.

Disclosure: The authors report no conflicts of interest.

Key points: -This study provides interesting preliminary data that may justify a larger clinical trial to examine the benefit of corticosteroids administered promptly after the onset of radicular low back pain.

Background

Low back pain is common

Although prevalence estimates vary, one-quarter of adults suffer at least one day of back pain in a three month period[1] and most adults suffer low back pain during their lives[2]. A subset of patients with low back pain have radicular symptoms, which are often attributable to specific spinal pathology such as a herniated intervertebral disc[3]. Determining the precise cause of radicular low back pain in young, healthy patients is unnecessary because initial medical management is identical, once infectious, neoplastic, rheumatological, and vascular pathologies have been excluded[3].

Medical management of low back pain is difficult

Despite optimal treatment, persistent pain or functional disability one month after an initial episode occur in two-thirds of patients who present to a medical provider[4-7]. Those with radicular signs or symptoms are at higher risk of poor outcome[4,7,8]. Effective interventions for this disease are needed.

Corticosteroids have long been hypothesized to be of benefit for radicular low back pain, although evidence supporting this hypothesis has been mixed. Hebedoe tapered high dose dexamethasone over one week in hospitalized patients with radiculopathy and found benefit of steroids at 9 days (absolute risk reduction: 33% (95%CI: 3, 63%), though this benefit had dissipated by 3 months[9]. Porsman, using an identical protocol in a similar population found no difference at 9 days[10]. Haimovic reported a statistically nonsignificant tendency toward early improvement in patients with pain on a straight leg raise test (absolute risk reduction 25% (95%CI: -12, 62%)[11]. Finckh identified a transient benefit of intravenous methylprednisolone in patients hospitalized with sciatica [12]. The value of local delivery of corticosteroids to the putative anatomical source of pain has also demonstrated mixed results, although in a highly selected population[13,14].

Based upon the suggestion of early benefit, we tested the efficacy of corticosteroids in a population of patients with radicular low back pain. Though the benefit may be only more rapid relief of pain and return to usual activities, it was felt to be worth pursuing, as long as the side effect profile of the intervention was minimal. To do this, we made two substantial modifications to the protocols of prior investigators. First, we reasoned that, as with other neurological processes, a benefit was most likely to be found if intervention was initiated early in the course of the disease symptomatology. Second, we also reasoned that if the only benefit to be found was earlier relief of symptoms, it would be important to minimize the toxicity of the intervention. With this in mind, we hypothesized that one 160mg dose of a long-acting form of methylprednisolone, in addition to standard care, would improve pain intensity scores one month after treatment in a population of healthy patients presenting to an Emergency Department (ED) with acute radicular low back pain. Pain was measured using an 11-point verbal numerical rating scale. Secondary outcomes, listed in greater detail below, included analgesic use and functional outcome assessments one month after ED discharge.

Methods

Overview

This was a randomized, placebo-controlled trial testing the efficacy of a long-acting form of methylprednisolone as adjuvant therapy for the treatment of acute radicular low back pain. Methylprednisolone acetate has a half life of 139 hours and is often administered on a weekly basis[15]. The 160mg intramuscular dose used in this trial is roughly equivalent to a daily oral dose of 20mg of methylprednisolone[15]. This study was approved by the Institutional Review

Board of Montefiore Medical Center. It was registered online at www.clinicaltrials.gov (identifier-NCT00290589).

Study population

Our study population consisted of young adults with recent (≤ 7 days) onset of low back pain who presented for treatment to an ED. Low back pain was defined as pain initiating from the area below the tips of the scapulae and above the buttocks. Patients younger than 21 years were excluded from the study for logistical reasons—the pediatric emergency department is located in a physically distinct location in our hospital. Patients older than 50 were excluded to minimize the likelihood of enrolling patients with pathological causes of low back pain. Patients were included only if their back pain had lasted one week or less, because of our belief that the intervention was most likely to work early in the course of the illness. Patients with recurrent back pain, defined for the purpose of this study as any other episode of back pain within the preceding month, were excluded for the same reason.

Patients were included only if they had a positive result on a straight leg raise test, a readily available, straightforward, and widely used clinical test to differentiate radicular from non-radicular low back pain. Controversy exists as to how best to perform this test and its test characteristics[16]. For the purpose of this study, we defined a positive straight leg raise test as pain radiating below the knee when either leg was raised to an angle between 30 degrees and 70 degrees, a range we believe to be most strongly associated with herniated intervertebral disc. The parameters that we used for a positive test are narrow and may not be accepted by all—there is not consensus on this subject. Our straight leg raise parameters allowed us to define a homogenous study population, but excluded from the study some patients who may have benefited. Standardization of this test was ensured by training all research personnel with a protractor, and making this instrument available.

Patients were excluded for temperature >37.9 degrees C, risk of pathological processes, such as a neoplasm known to metastasize, recent direct blunt trauma to the back, any chronic pain syndrome, a history of spinal surgery, an inflammatory arthritis, recent use of corticosteroids, use of pain medication on a daily or near daily basis, pregnancy, lactation, or allergy to protocol medications. Diabetics were not excluded.

Study setting and study personnel

This study was conducted in the ED of Montefiore Medical Center, the teaching hospital of the Albert Einstein College of Medicine. The ED sees an urban population, consisting mostly of underserved minorities. The annual adult census is 80,000 visits. Data were collected by salaried, fluently bilingual (Spanish and English) trained research associates who were present in the ED 24 hours per day, seven days per week.

Investigational protocol

Prior to discharge from the ED, potentially eligible patients were approached for participation in the study. The on-duty research associate explained the study to patients, screened for eligibility, and then asked for their written permission to participate in the study as a research subject. The research associates were specifically trained for this consent process and have passed required ethics coursework. Subjects were asked a series of questions about their pain, socio-demographic characteristics, and past medical and psychiatric history, which were answered orally. The subject was then administered 160mg of methylprednisolone acetate or placebo as one intramuscular dose by the clinical nurse. All study subjects were given a “back pack”, containing 14 pills of naproxen 500mg, to be taken twice daily on a full stomach, 14 pills of oxycodone 5mg/ acetaminophen 325 mg, to be taken as needed for pain, and a standardized back pain instruction sheet. Non-steroidals are first-line treatment for low back

pain[17]. Beyond this, it is unclear which medications should be used for treatment of back pain. We chose to include an opioid analgesic for breakthrough pain, rather than a muscle relaxant, because we felt the opioids would be useful for any patient with refractory pain and the muscle relaxant to be of less consistent efficacy[18].

Randomization and blinding

The methylprednisolone acetate or placebo was placed into sequential unmarked syringes by the research pharmacist in an order determined by a random number generator available online (www.randomization.com). The pharmacist did this in a location removed from the ED and inaccessible to ED personnel. The research syringes were then used in order by the clinical team. Double blinding and allocation concealment were ensured by using a comparable volume of placebo and by covering each syringe with an opaque wrap. Neither the study personnel, the clinical team, nor the research subject knew to which arm the subject was assigned or what medication the subject received. As a final precaution against un-blinding, the follow-up assessment was performed by an individual not associated with the clinical care of the patient.

Outcomes

The primary outcome for the study was pain intensity one month after ED discharge. Using an 11-point numerical rating scale (NRS), on which zero is no pain and ten is the worst pain imaginable, subjects were asked to report their worst pain over the previous 24 hours when contacted one month after ED discharge. The one month pain intensity score was standardized by subtracting it from that individual's baseline pain score, obtained at the time of ED triage. This method of subtracting a follow-up pain score from an initial score is a validated method of determining clinically important changes in pain intensity[19,20] and is used in low back pain clinical research[8]. Secondary outcomes at one month included presence or absence of back pain within the previous 24 hours, need for analgesics within the previous 24 hours, presence or absence of back pain over the preceding week, score on the Roland-Morris-18 functional disability scale[21], which assesses the impact of pain on typical daily activities, rate of return to usual activities and work and need to visit another medical provider. Pain intensity scores and score on the Roland-Morris-18 functional disability scale were also assessed one week after ED discharge. Finally, adverse medication effects were elicited by telephone using an open-ended question one week after ED discharge and by reviewing the subject's medical record.

Data collection and processing

Standardized paper data collection instruments were used to collect data in the ED and over the phone one month after ED discharge. All data were entered into SPSS Data Entry V.4.0 (SPSS Inc., Chicago, Illinois) by a research secretary, then double-checked for accuracy by the principal investigator, who remained blinded during this process.

Analysis

The primary planned analysis was a Student's t test for independent samples used to compare the between group difference in change in NRS score between ED visit and one month post-ED discharge ($NRS_{ED} - NRS_{1\text{month}}$). The Mann-Whitney U test was used for non-parametric data. The Kolmogorov-Smirnov test was used to determine whether the data deviated from the normal distribution. Proportions were compared using the chi-square test. Differences between proportions (absolute risk reduction) and odds of poor outcomes are presented with 95% CI. Analyses were performed using SPSS V.13 (SPSS Inc., Chicago, Illinois).

Sample size calculation

Based on previous work, we assumed a normal distribution and an NRS standard deviation of 3.0. With a two-sided $\alpha=0.05$, a sample size of 38 subjects in each group would give us a power of 0.8 to detect a difference of 2.0 in the primary outcome ($\text{NRS}_{\text{ED}} - \text{NRS}_{1\text{month}}$). We chose an NRS change of 2.0 as a cut-off for our study because it has robust clinical significance[22].

Results

Over a 4 year period beginning in July 2003, 637 patients were approached for participation and 82 were randomized. Please see a CONSORT flow diagram (Figure 1). Baseline characteristics were comparable between the two groups (Table 1).

One month after ED discharge, pain scores in the methylprednisolone group improved by a mean of 1.3 more than that in the placebo group (95% CI: -0.2, 2.7). Because these data were skewed (many patients improved completely), the Mann-Whitney U statistical test was used, resulting in $p=0.10$. The median improvement in pain scores was 2.0 more in the methylprednisolone group than in the placebo group. Secondary outcomes at one month are presented in Table 2.

One week after ED discharge, pain scores in the methylprednisolone group had improved by a mean of 1.1 more than placebo (95%CI -0.5, 2.8) and a median of 1.0 more than placebo ($p=0.16$). Any disability was reported by 42% of methylprednisolone subjects and 61% of placebo subjects (difference=19%, 95%CI: -4, 42%).

One week after investigational medication administration, adverse effects were reported by 32% of the methylprednisolone and 24% of the placebo patients (95%CI for difference of 9%: -12%, 30%). This included drowsiness in six methylprednisolone patients and five placebo patients, stomach pain in four methylprednisolone patients and two placebo patients, mood changes in one methylprednisolone patient and bloating in one placebo patient. There were no reports of gastro-intestinal bleeding, osteonecrosis, infection, complications of glucose metabolism, or requirement of additional medical treatment attributable to the investigational medication.

One month after ED discharge, subjects were asked whether they had seen another healthcare provider for treatment of their back pain. Of the methylprednisolone patients, 67% reported no further contact with a health care provider, compared with 59% of the placebo patients (95% CI for difference of 8%: -14, 30%). Of the methylprednisolone patients, 21% had seen their primary care provider, 6% had seen a back surgeon, and 3% had seen a physical therapist. Of the placebo patients, 28% had seen their primary care provider, 10% had seen a physical therapist and 3% had seen a physiatrist.

Discussion

We did not find a statistically significant difference in the primary outcome between the two arms. However, there were some suggestive features in the data. The 95%CI for the primary pain outcome tilted towards benefit of methylprednisolone, as did several of the secondary outcomes, such as use of analgesic medication in the previous 24 hours and occurrence of back pain in the previous week. The RM-18 functional disability scale demonstrated a statistically significant benefit of methylprednisolone. Given these data, it is not unreasonable to speculate that methylprednisolone acetate may be an efficacious treatment. Continued improvement in the intervention group relative to the placebo group beyond the one week window of expected efficacy of methylprednisolone supports the hypothesis that methylprednisolone may alter the underlying disease pathogenesis in certain subjects.

When using pain intensity scales such as the numerical rating scale, which have no inherent clinical significance, it is important to understand the clinical significance of the finding. In ED-based pain studies, an improvement of 1.3 units has been shown to be the smallest difference associated with a patient's report of improvement in pain [19,20]. However, in outpatient back pain trials, the minimum clinically important difference may be considerably higher[23]. Thus, even beyond question of statistical significance, the clinical importance of the difference of 1.3 units discovered in this work remains to be elucidated.

We identified four prior randomized trials of systemic corticosteroids for radicular low back pain. Three used a high-dose dexamethasone taper in patients who were hospitalized with radicular low back pain[9-11]. Overall, there was no benefit for patients randomized to the corticosteroid one week after enrollment (Summary odds of substantial improvement: 1.43 [95%CI: 0.51 to 3.98]). One author reported improvement three months after study enrollment in 32% of 19 patients randomized to corticosteroids and 25% of 20 subjects who received placebo[9]. Another author reported improvement one year after study enrollment in 29% of 21 subjects randomized to corticosteroids and 33% randomized to placebo[11]. None of these differences were statistically significant, though these studies lacked sufficient power. One author reported a transient benefit of intravenous methylprednisolone in patients hospitalized with sciatica, though this benefit had dissipated within several days[12]. Using some of this evidence, a US government sponsored guideline committee concluded that corticosteroids should not be used for low back pain[24]. Our study population is unique in that the intervention was initiated earlier after the development of symptoms, the patients were less disabled (none required hospitalization) and the population was not subject to the same degree of specialty practice selection bias. Further work, utilizing a similar population of patients, is required.

The magnitude of the disease burden is apparent from an examination of the placebo arm: 1/2 of patients still report functional disability from their back pain one month after the initial ED visit; 1/4 have not yet been able to return to their usual activities. Emergency physicians and other clinicians who treat this condition should bear this relatively poor short-term prognosis in mind.

The criteria for this study were highly restrictive, resulting in the need to screen almost eight low back pain patients for every one that was enrolled. We believed this to be necessary in order to obtain a homogeneous group of patients who were likely to be suffering from an acutely herniated disc. These results cannot be generalized to patients without a positive straight leg raise test. We excluded patients older than 50 to minimize the risk of enrolling a patient with underlying malignant spinal pathology so our results should not be generalized to those older than 50.

Limitations of this work include the sample size. This study was underpowered for the difference between groups that we observed. We based the sample size calculation on an estimate of the difference between pain scores of 2.0 NRS units[22], a value that has been suggested as a clinically robust difference. However a more commonly used estimate in ED-based pain studies is a value of 1.3 NRS units. In order to detect this difference at the conventional significance level of 0.05, we would require slightly more than 200 subjects.

A second limitation of this work is the dose of methylprednisolone acetate used. A dose was chosen that we believed would minimize type two error without exposing our subjects to undue harm. Because this dose was well-tolerated, we would use the same dose in future work.

Fifty-one patients were eligible to participate in this study but were not randomized because they refused to participate or because there was a logistical impediment, such as unavailability of investigational medication. We did not collect data on these patients. Thus, we are not certain

our study cohort mirrors a true population of young adults who present to an urban ED with radicular low back pain.

Finally, as the study required four years to complete, it is possible that there were changes in the data collection and secular trends that could affect findings such as changes in care for the control group. However the investigational protocol was strictly adhered to through on-going training of the research associates. Further, the research environment and clinical practices for treating radicular low back pain were stable during this time period.

In conclusion, this study was a negative study, though there was a suggestion of benefit of methylprednisolone acetate in a population of young adults with acute radicular low back pain. Further work with a larger sample of patients is needed.

Acknowledgments

Dr. Friedman is supported through a career development award (1K23NS051409) from National Institute of Neurological Disorders and Stroke

References

1. Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates: estimates from U.S. national surveys, 2002. *Spine* 2006;31(23):2724–7. [PubMed: 17077742]
2. Frymoyer JW, et al. Risk factors in low-back pain. An epidemiological survey. *J Bone Joint Surg Am* 1983;65(2):213–8. [PubMed: 6218171]
3. Deyo RA, Weinstein JN. Low back pain. *N Engl J Med* 2001;344(5):363–70. [PubMed: 11172169]
4. Cherkin DC, et al. Predicting poor outcomes for back pain seen in primary care using patients' own criteria. *Spine* 1996;21(24):2900–2907. [PubMed: 9112715]
5. Croft PR, et al. Outcome of low back pain in general practice: a prospective study. *BMJ* 1998;316:1356–1359. [PubMed: 9563990]
6. Pengel LHM, et al. Acute low back pain: a systematic review of its prognosis. *BMJ* 2003;327:323–327. [PubMed: 12907487]
7. Roland M, Morris R. A study of the natural history of low-back pain. Part II: Development of guidelines for trials of treatment in primary care. *Spine* 1983;8(2):145–150. [PubMed: 6222487]
8. Thomas E, et al. Predicting who develops chronic low back pain in primary care: a prospective study. *BMJ* 1999;318(7199):1662–7. [PubMed: 10373170]
9. Hedeboe J, Buhl M, Ramsing P. Effects of using dexamethasone and placebo in the treatment of prolapsed lumbar disc. *Acta Neurol Scand* 1982;65(1):6–10. [PubMed: 7039210]
10. Porsman O, Friis H. Prolapsed lumbar disc treated with intramuscularly administered dexamethasonephosphate. A prospectively planned, double-blind, controlled clinical trial in 52 patients. *Scand J Rheumatol* 1979;8(3):142–4. [PubMed: 386492]
11. Haimovic IC, Beresford HR. Dexamethasone is not superior to placebo for treating lumbosacral radicular pain. *Neurology* 1986;36(12):1593–4. [PubMed: 2946981]
12. Finckh A, et al. Short-term efficacy of intravenous pulse glucocorticoids in acute discogenic sciatica. A randomized controlled trial. *Spine* 2006;31(4):377–81. [PubMed: 16481946]
13. Koes BW, et al. Efficacy of epidural steroid injections for low-back pain and sciatica: a systematic review of randomized clinical trials. *Pain* 1995;63(3):279–88. [PubMed: 8719528]
14. Watts RW, Silagy CA. A meta-analysis on the efficacy of epidural corticosteroids in the treatment of sciatica. *Anaesth Intensive Care* 1995;23(5):564–9. [PubMed: 8787255]
15. Depo-Medrol package insert. [July, 2007]. Available at http://www.pfizer.com/files/products/uspi_depo_medrol.pdf
16. Deville WL, et al. The test of Lasague: systematic review of the accuracy in diagnosing herniated discs. *Spine* 2000;25(9):1140–7. [PubMed: 10788860]
17. van Tulder MW, et al. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2000;(2):CD000396. [PubMed: 10796356]

18. van Tulder MW, et al. Muscle relaxants for nonspecific low back pain: a systematic review within the framework of the Cochrane collaboration. *Spine* 2003;28(17):1978–92. [PubMed: 12973146]
19. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Ann Emerg Med* 2001;38(6):633–8. [PubMed: 11719741]
20. Todd KH, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996;27(4):485–9. [PubMed: 8604867]
21. Stratford PW, Binkley JM. Measurement properties of the RM-18. A modified version of the Roland-Morris Disability Scale. *Spine* 1997;22(20):2416–2421. [PubMed: 9355224]
22. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emerg Med J* 2001;18(3):205–7. [PubMed: 11354213]
23. van der Roer N, et al. Minimal clinically important change for pain intensity, functional status, and general health status in patients with nonspecific low back pain. *Spine* 2006;31(5):578–82. [PubMed: 16508555]
24. Bigos, SJ., et al. *Acute Low Back Problems in Adults*. Vol. 14. Rockville, Maryland: Agency for Health Care Policy and Research; 1994.

Figure 1.
CONSORT flow diagram

Table 1

Baseline characteristics

	Methylprednisolone (n=39)	Placebo (n=43)
Female gender	54%	51%
Race/Ethnicity ¹ :		
African-American/Black	22%	21%
Asian	0%	2%
Hispanic/Latino	69%	67%
White	8%	7%
Other	0%	2%
Age (mean [SD])	39 (9)	37 (8)
Duration of back pain in hours (median[IQR])	48 (24, 72)	48 (14, 72)
Arrived by EMS	6%	13%
Pain intensity at ED triage (mean[SD]) ²	8.9 (1.2)	9.1 (1.1)
Pain intensity at ED discharge (mean [SD]) ²	8.1 (2.0)	8.3 (1.7)
Body mass index (Kg/M ²) (mean [SD])	28.1 (6.1)	28.5 (5.8)
History of bipolar disease	8%	3%
Full-time employment	74%	73%

¹ As determined by patient self-report

² As reported by the patient on a scale from 0 to 10, with 10 representing the worst pain imaginable

Table 2

One month outcomes

	M-Prd ¹ (n=37)	Placebo (n=41)	Difference (95%CI)	p	OR (95%CI)
Mean (SD) decrease in pain, ED visit to one month (NRS _{ED} - NRS _{1month}) ²	7.1 (3.0)	5.8 (3.5)	1.3 (-0.2, 2.7)	0.10	NA
Any occurrence of back pain over the previous 24 hours	46%	61%	15% (-7, 37%)	0.18	0.54 (0.22, 1.3)
Analgesic use in the previous 24 hours	22%	43%	20% ³ (0, 40%)	0.06	0.39 (0.14, 1.1)
Any occurrence of back pain over the previous week	47%	68%	20% ³ (-2, 40%)	0.07	0.43 (0.17, 1.1)
Roland-Morris18 disability scale ⁴					
-Median (IQR)	0 (0.0)	0 (0.11)	NA	0.009 ⁶	NA
-Any disability ⁵	19%	49%	29% ³ (9, 49%)	0.007	0.25 (0.09, 0.7)
Not yet resumed usual activities	14%	23%	9% (-9, 27%)	0.34	0.56 (0.17, 1.9)
Not yet resumed work (of full-time workers)	2/24 (8%)	3/24 (13%)	4% ³ (-13, 21%)	0.64	0.64 (0.10, 4.2)

¹ M-Prd=Methylprednisolone acetate

² This is the primary outcome. Higher values indicate greater relief of pain.

³ Because we rounded to whole numbers, difference cannot be calculated by subtracting column 2 from column 3

⁴ Higher values indicate greater functional disability. IQR=inter-quartile range. These values represent the actual one month score.

⁵ Disability was defined as an affirmative response to any one of the 18 Roland-Morris questions

⁶ Determined using the Mann-Whitney U test