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Original article

SLA-VER: study protocol description and preliminar results of the first italian RCT on conservative treatment of distal radial fractures

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Summary. *Introduction:* There is no consensus on which is the best way to maintain initial reduction of a distal radius fractures (DRFs). The aim of this study is to test the hypothesis that below elbow cast (BEC) is equivalent to above elbow cast (AEC) in maintaining initial reduction of DRFs. This paper will report on midterm results. *Methods:* SLA-VER is a prospective, monocentric, randomized, parallel-group, open label, blinded endpoint evaluation non-inferiority trial (PROBE design) comparing the efficacy of AECs and BECs in DRFs conservative treatment in terms of loss of radial height (RH), radial inclination (RI) and volar tilt (VT) during cast immobilization (average 35 days) of 353 consecutive DRFs. Non-inferiority thresholds are 2 mm for radial height, 3° for radial inclination and 3° for volar tilt. Study population will be 353 patients, randomized into 2 groups (AEC vs BEC). One-hundred patients have completed the study so far. *Results:* Patients in BEC group lost 1,75 mm of RH, 2,9° of RI and 4,5° of VT over the course of cast immobilization. Patients in AEC group lost 1,71 mm of RH, 2,2° of RI and 4,8° of VT. Raw differences between average loss of RH, RI, VT during treatment between study groups were respectively 0,04 mm, 0,7° and 0,3°. Logistic and ANCOVA models have been used to correct for confouding variables. *Conclusions:* Difference of loss of RH, RI and VT between the two groups are all below the non inferiority thresholds. Cast type does not seem to affect maintenance of reduction in conservatively managed DRFs. (www.actabiomedica.it)

Key words: distal radius fracture, cast, above-elbow cast, below-elbow cast, short arm cast, long arm cast

Introduction

Distal radius fractures (DRFs) represent a common clinical challenge in the everyday practice of an orthopaedic trauma department. The rising number of people affected by DRFs is most likely due to an aging population and the necessity of understanding the best possible treatment for these lesions is mandatory (1, 2). The absence of a consensus strategy has negative implications for the management of these common lesions, particularly in terms of quality of care and highest patient comfort. Optimal standard care for DRFs that are deemed to be treated conservatively has long been a matter of controversy. Currently, there is no general agreement on how to immobilize a DRF. Various methods have been described, but any approach has been proved more effective than the others (3-6). The latest clinical practice guidelines of the American Academy of Orthopaedic Surgeons, released in 2009, labeled the evidence available for or against elbow immobilization in patients treated with cast as "inconclusive", leaving the choice between them to the clinician's judgment (7). We designed a RCT to compare the two treatments. The Short vs- Long Arm cast, the

VERona trial (code name SLA-VER), expected to last 30 months and recruiting 353 patients randomly assigned to below-elbow cast (BEC) and above-elbow cast (AEC) will hopefully give guidance on the role of cast type in DRFs conservative treatment. This RCT, started at our institution on March 15th 2017, has until now recruited 162 patients. Recruitment is expected to be completed by 2019 and final results published by 2020. This paper will report on the midterm results of the study.

Methods

SLA-VER is a prospective, monocentric, randomized, parallel-group, open label, blinded endpoint evaluation non-inferiority trial (PROBE design) comparing the efficacy of AECs and BECs in DRFs conservative treatment. Its main goal is to test the non-inferiority of BECs as opposed to AECs to maintain reduction of manipulated DRFs. A secondary goal is to compare patient tolerability and quality of life of the two treatments. This study has been approved by the institutional review board of Verona and Rovigo (CE1165CESC) and registered on ClinicalTrials.org (NCT03468023). The study was conducted in accordance with the Declaration of Helsinki. All patients enrolled so far gave written informed consent. The study focused on the variation of radial height (RH), radial inclination (RI) and volar tilt (VT) over the course of treatment. To aimily reach 89% power to show any difference between the treatments with a two-sided type 1 error rate of 5%, we calculated that 150 patients would be required for each group using 2 mm difference in RH, 3° difference in RI and VT as non-inferiority thresholds. These estimates of minimal clinically relevant differences were based on previous reports of interobserver variability of up to 3° in radiographic parameter measurement and considerable deterioration of clinical outcome when loss of RH was more than 5 mm (8-10). We then added 53 additional patients to make up for an expected 15% loss of patients due to dropouts for a final study population of 353 patients. Based on a patient flow analysis we calculated to be able to complete recruitment in 30 months. All patients admitted to ER with a diagnosis of DRF were considered for recruitment in the study protocol if they met the following inclusion criteria: age ≥18 yrs; indication to conservative (nonoperative) treatment; displaced fracture requiring manipulation, patient's consent. Exclusion criteria were as follows: skeletally immature patient (age <18 yrs); undisplaced fracture not requiring manipulation; fracture requiring ORIF (e.g. Goyrand fractures); open fracture; any hand/wrist/forehand skin lesion on fractured limb; any vascular or neurological deficit; bilateral fracture; any association with homolateral upper limb fracture. Patient with any kind of medical comorbidities were included in the study; Patients exited the study (dropouts) when satisfactory reduction could not be achieved at first or second attempt (according to Graham's criteria), cast had been damaged or removed during treatment, or if they withdrew the consent (11). Software random allocation in blocks of 4 resulted in 353 sequentially numbered, opaque sealed envelopes. This was done by a statistician with no involvement in clinical care of patients. Radiographic measurements were all performed by a single investigator who was not involved in patient recruitment and was blinded to patient group assignement. Statistiscal analysis were carried out by statistician who was blinded to group assignement (BEC vs AEC). When a patient was eligible for enrollment and gave written consent to recruitment upon clear explanation of the study protocol, the treating physician opened an envelope and assigned the patient to the treating group. Closed manipulation of the displaced fractured was performed under local anaesthesia (haematoma block with 5-10 ml of mepivacaine 2%); the forearm was immobilized in opposite-to-the-dislocation position or neutral position in the case of severe metaphyseal comminution without angular deformity. Standard arm cast was a radial gutter manufactured using plaster of Paris. None of the fractures were treated in an operating room or using a C-arm image intensifier. Patient assigned to BEC group were treated with a below-elbow cast extending from the metacarpal heads to 2-4 cm from the elbow. Patient assigned to AEC group were treated with an above-elbow cast extending from the metacarpal heads to midway of the arm. X-rays (PA and LL views) were taken prior and after manipulation, at 7 and 35 days. The radial gutter was closed at first office visit and removed at the final one. Radiographic parameters were determined for each x-ray examination from the time of injury to the end of treatment. Radial length (RL) was measured on the PA view as the distance between two lines drawn perpendicular to the radial shaft's long axis: one line was drawn at the tip of radial styloid and the other line was drawn at the ulnar border of radius articular surface at the central reference point (12). Radial inclination (RI) was measured on the PA view by determining the angle between a line passing through the tip of the radial styloid and the medial corner of the articular surface of the radius and a line perpendicular to the shaft ofthe radius. Volar tilt (VT) was measured on the LL view by the angle between the line of the distal articular surface (a line passing through the two most distal points of the dorsal and volar lips of the radius) and a line perpendicular to the longitudinal axis of the radius (Fig. 1, 2, 3). Fracture stability was assessed according to Lafontaine (dorsal angulation >20°, dorsal comminution, articular involvement, associated ulnar fracture, age >60 years) on pre-treatment radiographs: if three or more of these criteria were present, the fracture was defined as unstable (13). Cast index was determined, as described by Chess on post-reduction radiographs,

Figure 1. Radial Height measurement before and after reduction

Figure 2. Radial Inclination measurement before and after reduction

Figure 3. Volar Tilt measurement before and after reduction

as the ratio between the cast widths measured respectively on LL view and on PA view (14). Maintenance of reduction was considered acceptable when it met the following criteria described by Graham: loss of radial length <5 mm, radial inclination ≥15°, volar tilt between +15 and −20°. Patients were stratified by age, sex, presence of osteoporosis (indirectly assessed by osteoporosis-specifc drug consumption), fracture type (according AO classification) and fracture stability (according Lafontaine's criteria) (11, 13, 15). Protocol details are also available on https://clinicaltrials.gov/ct2/show/NCT03468023.

Statistical analysis

For comparisons of single continuous variables T-tests were used, for categorical variables the Chi-squared test (α=0,05) was used. To test the association of more than one variable simultaneously on dicotomicous variables a logistic model was performed. For continuous variables an ANCOVA model was used.

Results

Patient population and treatment assignement

One-hundred-sixty-two patients were recruited from March 2017 to June 2018. Of these, 140 have completed followup and were considered for analysis. Six patients have been enrolled by mistake (they were found not to meet inclusion/exclusion criteria), 4 were lost to follow up, 30 were dropouts (Tab. 1). Patients included in this analysis were 100 of which 50 patients assigned to BEC group and 50 patients to AEC group. Patients excluded from analysis were homogeneously distributed among the two treatment groups, leaving the remaining data sufficiently unbiased to undergo further statistical anaysis (Table 1). Demographic and baseline characteristics were again homogeneously distributed among the two groups. There are no significant differences in sex, age, fracture type, osteoporosis, fracture stability. Characteristics of patients by treatment group are summarized in Table 2. Chi-squared tests were performed to test each variable association with treatment, none of them is significant (assuming α=0.05). We additionally performed a logistic model to test the association between all pretreatment variables and group assignement. No variables have been found to be statistically associated to treatment group assignement (α=0.05).

Table 1. Dropouts and patients excluded from analysis. No statistical difference between the treatment groups (Fisher test=0.96, pvalue>0.05)

	Treatment		
	BEC	AEC	Total
Dropout			
Skin lesion occured during manipulation		1	1
Manipulation unsuccesful	9	8	10
Cast damaged/removed	5	7	12
Excluded from analysis			
Enrolled by mistake	3	3	6
Lost to followup	3	1	4
Tot	**20**	**20**	**40**

Radiographic parameters

Mean time of cast immobilization for patients included in the analysis treated with a below-elbow cast was 32,1 days (5-56 days), for patients treated with an above-elbow cast was 31 days (39-7 days). Radiographic parameters are summarized in Table 3. T-test between treatment groups at baseline did not show any statistically significant difference (α=0,05). Baseline radiographic parameters were measured on post-reduction xray taken on the day of enrollment in the study and compared with those measured on final xray taken on the last followup visit

Non inferiority thresholds

For each radiographic parameter we compared post reduction measurements with baselines values for each patient (Δ), then we calculated treatment groups means and the difference between them. An example of the formulas used for Radial Length (group A is BEC, group B is AEC):

$$\Delta_{RL} = RL_{post-reduction} - RL_{baseline}$$

$$raw\ diff = group\ A\ mean(\Delta_{RL}) - group\ B\ mean(\Delta_{RL})$$

Table 2. Characteristics of patients by treatment group. Randomization created two homogeneous groups by major confounders (sex, age, AO type, osteoporosis and stability)

	BEC (n=50)	AEC (n=50)	Chi-square test, p-value
Sex			p=0,56440
Male	6 (12%)	8 (16%)	
Female	44 (88%)	42 (84%)	
Age			p=0.7180
yrs (CI 95%)	70 (66,1-74,1)	68 (63,9-72,6)	
AO Type			p=0.2640
A	30 (60%)	25 (50%)	
B	0 (0%)	2 (4%)	
C	20 (40%)	23 (46%)	
Osteoporosis			p=0.6870
Yes	21 (42%)	23 (46%)	
No	29 (58%)	27 (54%)	
Stability (La Fontaine criteria)			p=0.6892
Stable	26 (52%)	24 (48%)	
Unstable	24 (48%)	26 (52%)	

Table 3. Radiographic parameters measured at baseline a final xray, divided by treatment group. We reported mean values and 95% confidence Intervals. For all variables confidence intervals overlap

	BEC (mean [95% CI])	**AEC (mean [95% CI])**
Baseline Xray		
Radial height (mm)	10,8 [10,3; 11,4]	11,5 [11,1; 12]
Radial inclination (°)	20,5 [19,4; 21,5]	22 [21,1; 22,8]
Volar tilt (°)	-7,6 [-9,4; -5,8]	-6,6 [-8,1; -5]
Final Xray		
Radial height (mm)	9,3 [8,7; 9,9]	10,2 [9,6; 10,7]
Radial inclination (°)	17,8 [16,8; 18,8]	20,2 [19,3; 21,1]
Volar tilt (°)	-3,7 [-6,7; -0,7]	-2,1 [-4; -0,1]

Table 4. Differences between AEC and BEC group calculated raw or with ANCOVA models corrected by measurable confounders

	Raw difference post reduction variables[1]	Difference corrected by all variables[2]	Difference corrected by	Non-inferiority threshold
Radial length	0.04	0.18	0.16	2 mm
Radial inclination	0.7	0.78	0.94	3°
Volar tilt	0.18	0.15	0.24	3°

[1] Variables included as covariates in the ANCOVA model: cast index, reduction quality and cast quality.

[2] Variables included as covariates in the ANCOVA model: cast index, reduction quality and cast quality, days to final followup, AO Type, sex, osteoporosis, stability, age

Taking into account raw data, patients in BEC group lost 1,75 mm of RH, 2,9° of RI and 4,5° of VT over the course of cast immobilization. Patients in AEC group lost 1,71 mm of RH, 2,2° of RI and 4,8° of VT. For all radiographic parameters we obtained raw differences between groups. In order to control for possible bias due to measured variables we corrected these differences using an ANCOVA model for post reduction (cast index, reduction quality and cast quality) and pre reduction variables (sex, age, fracture type, osteoporosis, fracture stability). Results are summarized in Table 4. Values are reported in comparison with non-inferiority thresholds used in the SLAVER protocol: all differences are below the correspondent threshold. Raw differences between average loss of RH, RI, VT during treatment between the two groups were respectively 0,04 mm, 0,7° and 0,3°.

Discussion

Distal radius fractures represent a common clinical challenge in the everyday practice of an orthopaedic trauma department.

The absence of a consensus strategy has negative implications for the management of these common lesions, particularly in terms of quality of care and highest patient comfort.

Currently, there is no general agreement on how to immobilize a DRF. Various methods have been described, but no one approach has been proved more effective than the others.

Sarmiento in 1975 and later Bünger in 1984 proposed the use of a long-arm cast to lock the forearm in supination to neutralize the brachioradialis muscle, which was considered responsible for loosing reduction. Based on electromiographic studies, Sarmiento argued that immobilizing the wrist in supination, with brachioradialis in a resting position, would minimize the muscle influence on fracture displacement (3, 5). Wahlstrom proposed the pronator quadratus muscle as a major deforming force, thus suggesting locking the wrist in pronation (6). This was based on the assumption that even minimal movements of the distal radio-ulnar joint could endanger the maintenance of reduction. However, there is no evidence that locking prono-supination plays a role in maintaining reduction. Indeed, many prospective randomized trials have failed to support this theory, concluding that there is no difference in the risk of secondary displacement with or without elbow immobilization (16-21). However, most of these reports were biased and lacking statistical evidence, thus preventing clinicians from putting these findings into practice. In 2003, a Cochrane review concluded that there was insufficient evidence to make any recommendations as to what is the best conservative treatment for DRFs (22).

A previous retrospective study conducted at our institution did not show any difference in rate of secondary displacement in DRFs managed either with BEC or AEC. We observed that average difference in reduction maintenance probability between the two groups at 35 days was 1.2%. This finding led us to hypothesize that the two treatments were substantially equal (23). However, case series studies result in only level III clinical evidence which is insufficient to draw scientifically sound conclusions.

SLAVER was designed to further support the hypothesis that type of cast does not affect the likelihood of secondary displacement in conservatively managed DRFs. We planned this study as a non-inferiority trial, hence we established non-inferiority thresholds as described above. If any study outcome variable (namely, RH, RI, VT) was not above the non inferiority threshold one could reasonably assume that no actual difference exist. Likewise, if 95% confidence intervals overlapped no difference between groups is assumed. Quality of randomization was checked with chi-square tests and logistic models to make sure no variables were associated with patient group assignement. To remove any confounding variable and ensure study variable was dependant solely on type of cast, ANCOVA models were used to correct results by all confounding variables. These preliminary results show that the difference of loss of RH, RI and VT between the two groups are all below the non-inferiority thresholds: the two treatments did not differ for more than 2 mm of loss for radial height, 3° of loss for radial inclination and volar tilt. This would indicate a possible clinical equivalence of the two treatments. However, sample size is not large enough to achieve statistical significance.

Currently, two more RCTs on the same topic are underway in Brasil and North America (24, 25).

The best conservative treatment of DRFs remains still to be understood. Results from our RCT along with the brasilian and north american RCTs will help provide additional evidence on the role of cast length to treat DRFs in the hope of moving closer to high quality guidelines.

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