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Fluoxetine and fractures after stroke: **exploratory analyses** from the FOCUS trial.

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Cover title

Fluoxetine and fractures after stroke. FOCUS trial

Tables 2; Figure 1.

Key Words

Stroke, Fluoxetine, Fractures, Randomised controlled trial, Falls

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2000

Abstract

Background and purpose

The FOCUS trial showed that fluoxetine did not improve modified Rankin scale scores (mRS) but increased the risk of fractures. We aimed to describe the fractures, their impact on mRS and factors associated with fracture risk

Methods

A UK, multicentre, parallel group, randomised, placebo-controlled trial. Patients ≥18yrs with a clinical stroke and persisting deficit assessed two to 15 days after onset were eligible. **Consenting** patients were allocated fluoxetine 20mg or matching placebo for six months. The primary outcome was the mRS at six months and secondary outcomes included fractures.

Results

Sixty five of 3127(2.1%) patients had 67 fractures within six months of randomisation; 43 assigned fluoxetine and 22 placebo. Fifty nine (90.8%) had fallen and 26(40%) had fractured their neck of femur. The effect of fluoxetine on mRS (Common odds ratio (COR)=0.951) was not significantly altered by excluding fracture patients (COR=0.961). Cox proportional hazards modelling showed that only age >70yr (Hazard Ratio (HR)=1.97(95% CI 1.13 to 3.45;p=0.017), female sex (HR=2.13(1.29 to 3.51;p=0.003) and fluoxetine (HR=2.00(1.20 to 3.34;p=0.008) were independently associated with fractures.

Conclusions

Most fractures resulted from falls. Although many fractures were serious, and likely to impair patients' function, the increased fracture risk did not explain the lack of observed effect of

fluoxetine on mRS. Only increasing age, female sex and fluoxetine were independent predictors of fractures.

Clinical trial registration

URL:http://www.controlled-trials.com. ISRCTN83290762

Introduction

Stroke survivors are at greater risk of fractures compared with stroke free individuals[1]. Many stroke survivors become depressed and are treated with selective serotonin reuptake inhibitors (SSRIs) which have been associated with higher risk of bone fractures in observational studies.[2] Mechanisms include increased risk of falling as well as effects of stroke and SSRIs on bone density.[3] These observational studies are confounded by indication, since depression is associated with increased fractures risk.[4]

The FOCUS trial aimed to establish whether fluoxetine improved the functional outcome (mRS) after stroke. It demonstrated no significant difference in mRS but fewer patients allocated fluoxetine developed new depression during six month treatment period (13.43% *vs* 17.21%; p=0.0033) and more patients in the fluoxetine group had fractures (2.88% *vs* 1.47%; p=0.0070)[5].

The FOCUS trial results strongly suggest that fluoxetine actually causes fractures. In these exploratory analyses of the FOCUS data we aimed to address the following questions:

1. What sites did fractures affect?
2. Did the excess of fractures obscure beneficial effects of fluoxetine on mRS?
3. What baseline factors were associated with fractures?
4. Does the timing of fractures provide clues to the potential mechanisms of SSRI induced fractures?

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. FOCUS was a multicentre, parallel group, randomised, placebo-

controlled trial which enrolled 3,127 patients in 103 UK hospitals. Patients ≥18 years old, with a stroke and focal neurological deficits persisting at two to15 days after onset were eligible. **Consenting** patients were randomly allocated fluoxetine 20 mg or matching placebo for six months. The primary outcome was the mRS, at six months. Patients, carers, health-care staff, and the trial team were blinded to treatment allocation. Details of fractures confirmed on X-Rays, were sought at hospital discharge and six months follow up. **The Scotland A Multicentre Research Ethics Committee approved the protocol on Dec 21,2011. Written consent was obtained from all patients, or a proxy if they lacked capacity.**

We compared the number of fractures occurring in those with and without specific characteristics (table 1) and formally tested each variable by plotting time to fracture on Kaplan-Meier survival curves in those with and without each characteristic and compared these with the log-rank statistic. We included all variables with a $p<0.1$ into a Cox proportional hazards model to identify independent predictors of fracture risk.

Results

Sixty five of the 3127(2.1%) patients enrolled had 67 definite new fractures (two patients sustained more than one fracture simultaneously) within six months of randomisation. This analysis excludes three patients reported previously whose fractures may have been present at randomisation.[5] Of the 67, 59(90.8%) resulted from a fall. The most common fracture sites were: neck of femur 26(40%), vertebral 10(15%), and wrist 7(11%) with 40(62%) affecting sites associated with osteoporosis.

Removing the 65 patients with a fracture from the primary analysis did not significantly alter the estimate of effect of fluoxetine on mRS (COR including fractures 0.951(95% CI 0.839 to 1.079];p=0.439) and 0.961(95% CI 0.847 to 1.093;p=0.545) without fractures).

Patients with fractures were older (mean age(sd) 76.2(11.6) vs 71.3(12.2), difference in mean 4.9(95% CI 2.0 to 7.9) p= 0.0012) but had similar NIHSS scores (median 7(IQR 4,11) vs 6(3,11), p=0.4065). The baseline characteristics of those with and without fractures are shown in Table 1. The Cox proportional hazards model showed that only age >70yr (Hazard Ratio (HR)=1.97(95% CI 1.13 to 3.45; p=0.017), female sex (HR=2.131 (1.294 to 3.511; p=0.003) and fluoxetine treatment (HR=2.00 (1.196 to 3.344;p=0.0082) were independent predictors of fracture (Table 2). The Kaplan Meier curve comparing fracture risk in the two treatment groups is shown in the Figure.

Discussion

The most common site of fracture was neck of femur, and most were in sites associated with osteoporosis; and almost all resulted from a fall. Removing patients who had fractures between randomisation and six months from our primary analysis did not greatly alter our estimate of the effect of fluoxetine on mRS. Older age, female gender and fluoxetine were independent predictors of subsequent fractures. An increased risk of falling is likely to explain much of the excess risk because most fractures were associated with a fall, falls with injury were more common in the fluoxetine group (120(7.67%) vs 94(6·01%) p=0.0663)[5] and the risks in the two treatment groups diverged early after randomisation (figure). No other baseline factors analysed had statistically significant associations with fracture risk.

Our analyses do not support the hypothesis that loss of function due to the excess of fractures in the fluoxetine group might explain the lack of improvement in functional outcomes

observed in the trial. Our finding that greater age, and female gender are associated with fracture risk confirms the findings of observational studies.[1] **This might be due to effects on cognition, coordination, balance, or activity levels on falls but we cannot exclude a contribution from fluoxetine's possible effect on bone density.**

These exploratory analyses have limitations. The number of falls and fractures were modest limiting the power of these analyses. **We did not collect many data items at baseline (e.g. balance), during the treatment period (activity, cognition) or at the time of a fall or fracture (e.g. current medication) which could have been associated with falls and/or fracture risk because these outcomes were not the focus of our trial.** Our only baseline indicators of bone density were previous fractures and the use of medications at baseline to reduce bone loss. Also, we did not systematically collect fractures beyond six months so cannot determine whether the effect of fluoxetine on fracture risk persists, as it might if it causes osteoporosis, or whether the risk subsides after stopping if it acted by causing falls directly, or indirectly.

The ongoing AFFINITY and EFFECTS trials will provide an opportunity to confirm our findings and further explore the mechanisms of fractures.[5] The risk of fractures with fluoxetine, especially in older female patients, needs to be considered when making decisions to use it after stroke.

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EL and PS contributed to trial design, commented on drafts and approved the submitted version of this report.

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Disclosures:

None

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Figure Legend

Kaplan-Meier curves comparing the risk of fracture in those allocated fluoxetine and placebo

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Table 1. The baseline characteristics of patients with and without fracture and Log rank statistic to provide a p value for the difference in Kaplan-Meier curves in those with and without each characteristic.

	No fracture		Fracture		Log-rank
Patient characteristics	N	%	N	%	Statistic (p)
All patients	3062	100.0	65	100.0	
Randomised treatment					
Fluoxetine	1521	49.7	43	66.2	0.0084
Placebo	1541	50.3	22	33.9	
Sex					
Female	1167	38.1	38	58.5	0.0005
Male	1895	61.9	27	41.5	
Age group					
≤70 years old	1313	42.9	17	26.2	0.0033
>70 years old	1749	57.1	48	73.9	
Before the stroke					
Dependent in activities of daily living	253	8.3	8	12.3	0.1762
Ischaemic stroke/TIA	557	18.2	11	16.9	0.8817
Diabetes	628	20.5	12	18.5	0.7603
Bone fractures	486	15.9	11	16.9	0.8285
Depression	244	8.0	9	13.9	0.0913
Stroke type					
Intracerebral haemorrhage	301	9.8	10	15.4	0.1320

Stroke deficits at baseline					
Unable to walk	2227	72.7	53	81.5	0.0849
Unable to lift both arms	1243	40.6	25	38.5	0.8704
Cannot talk	779	25.4	18	27.7	0.5203
Motor deficit on NIHSS	2665	87.0	57	87.7	0.7967
Visual field deficit on NIHSS	844	27.6	14	21.5	0.3261
Limb ataxia on NIHSS	753	24.6	17	26.2	0.8323
Baseline medications					
Non SSRI anti-depressant	137	4.5	5	7.7	
Treatments for Osteoporosis	287	9.4	5	7.7	
Major or minor tranquillisers	121	4.0	3	4.6	
Parkinsons disease medication	14	0.5	2	3.1	
BP lowering medication	2178	71.1	52	80.0	0.1000
Treatments for vertigo	129	4.2	5	7.7	
Any of these drugs of interest	2349	76.7	55	84.6	0.1161

Table 2. Cox proportional hazards models.

Variables	**Value**	**Pr>ChiSq**	**Hazard Ratio**	**95%CI**	
				Lower	Upper
Model including all variables					
Sex	Female	0.0082	1.978	1.193	3.280
Age	>70 years old	0.0181	1.973	1.123	3.467
Previous depression	No/UK	0.1348	0.581	0.285	1.184
Able to walk	No	0.2396	1.462	0.776	2.755
Randomised treatment	Fluoxetine	0.0086	1.992	1.191	3.330
Final model					
Sex	Female	0.0030	2.131	1.294	3.511
Age	>70 years old	0.0174	1.972	1.127	3.451
Randomised treatment	Fluoxetine	0.0082	2.000	1.196	3.344

Figure.