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Pilot Randomized Trial of Donepezil Hydrochloride for Delirium After Hip Fracture

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Abstract

Objectives—To determine whether donepezil hydrochloride can reduce the prevalence and severity of delirium among older patients undergoing hip fracture repair.

Design—Pilot double-masked randomized placebo-controlled trial.

Setting—Large academic medical center

Participants—Sixteen patients aged 70 and older with hip fracture

Intervention—Donepezil 5 mg or placebo was randomly allocated and initiated within 24 hours of surgery, preoperatively or postoperatively. Daily treatment was continued for 30 days or until side effects or the clinical situation required termination.

Measurements—All outcomes were ascertained masked to treatment status. Information on drug tolerability and safety was obtained from the patient, nurse, and medical record. Delirium presence and severity were measured during daily hospital interviews, and at 2, 4, and 6 weeks after surgery after a standardized assessment using the Confusion Assessment Method (CAM) and the Memorial Delirium Assessment Scale (MDAS).

Results—Patients in the donepezil and placebo arms had similar baseline characteristics. Patients in the donepezil arm experienced significantly more side effects, and a trend toward more serious adverse events. In longitudinal models, there were no significant differences between the donepezil and placebo (reference) arms with regard to delirium presence over time (odds ratio=0.9, 95% Confidence Intervals (CI): [0.4, 2.3]) or delirium severity over time (effect size=−0.2 on 30 point MDAS scale, 95% CI: [−1.5, 1.2]).

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Trial Registration: SHARP: Supporting Hip-fractured Adults through the Recovery Period is registered at www.clinicaltrials.gov (NCT00586196) and is no longer accepting participants.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Data access and integrity: Dr. Marcantonio had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conclusion—Patients randomized to donepezil had no significant improvement in delirium presence or severity, but experienced more side effects. Overall, we did not find sufficient evidence from our pilot to warrant a definitive Phase III trial.

Keywords

Delirium; Donepezil; Hip fracture; Randomized trial

INTRODUCTION

Delirium (acute confusion) is highly prevalent among hospitalized elders and is associated with substantial morbidity within the hospital and beyond (1). Certain patient populations are at high risk for poor outcomes after an episode of delirium. Among these are patients admitted for surgical repair of hip fracture, which annually affects over 350,000 older Americans and 1.66 million worldwide (2), and has been associated with 40–60% risk of delirium (3). We have previously shown that delirium independently predicts poor functional recovery after hip fracture, and that persistent delirium is associated with worse recovery than delirium that resolves quickly (4). We subsequently rigorously tested a model of proactive multifactorial geriatrics consultation that reduced the incidence of delirium by over one-third, and severe delirium by over one-half (5). However, once delirium developed, our intervention had no impact on the duration of delirium or its sequelae. These results parallel those of Inouye and others (6), and suggest that optimal delirium management requires additional strategies beyond multifactorial protocols.

One potential approach to enhance the management of delirium is drug treatment. However, because of the challenges working with a high-risk older hospitalized population, few rigorously performed trials of the pharmacological management of delirium have been performed. Moreover, most of these have focused on the control of acute agitation with anti-psychotics (7, 8), and have not addressed the underlying cognitive deficits that define the syndrome. Cholinesterase inhibitors are now commonly used to improve cognitive function in patients with Alzheimer's disease and related dementias by enhancing central cholinergic transmission (9). Delirium parallels dementia in that an acute deficiency in cholinergic transmission is felt to be a “final common pathway” leading to cognitive dysfunction (10). Despite this, there have been few published randomized trials examining treatment with cholinesterase inhibitors for delirium (11–13), and the results have been mixed, with one trial showing no effect (11) and another suggesting a potential benefit (12). Moreover, these trials were performed in patients undergoing scheduled orthopedic procedures, and excluded emergency hip fracture repair, which is the population at highest risk for delirium and its adverse outcomes. Therefore, we performed a pilot double-masked placebo-controlled randomized trial in hip fracture patients aged 70 and older. All participants received proactive geriatrics consultation and our trial tested whether the addition of a cholinesterase inhibitor (donepezil hydrochloride) resulted in reduced delirium presence and symptoms over time. As a pilot trial, our primary Aims were to assess participant accrual, drug tolerability and safety, and to obtain effect size estimates to determine whether a definitive Phase III clinical trial was warranted.

METHODS

Participant Eligibility Criteria

Subjects were individuals admitted to the orthopedics service of a large academic medical center for surgical repair of hip fracture. Eligibility requirements include age of 70 years or older, the ability to communicate effectively in English (including adequate hearing), residence within a 40 mile radius of the medical center to facilitate follow-up assessments,

life expectancy 6 months or greater, not currently on cholinesterase inhibitor therapy or with known hypersensitivity to cholinesterase inhibitors, and not a previous study participant or refusal. We also excluded patients with a pathologic fracture due to metastatic cancer, and those with advanced dementia or total functional dependence, who we felt had little potential for functional recovery.

Informed consent

Our trial was approved by the Institutional Review Board. Informed consent included permission to randomize to donepezil vs. placebo, and participation in the data collection protocol to evaluate study outcomes. For patients who were not capable of providing informed consent (because of dementia, delirium or both), we obtained proxy consent from the appropriate legally authorized representative. In these cases, we also required verbal assent or no active refusal by the subject.

Treatment protocol

Geriatrics Co-management—All hip fracture patients at our medical center are admitted to a geriatrics-orthopedics service, and therefore receive perioperative co-management by a clinical geriatrics team using our previously developed protocol (5). This ensures that all easily correctable factors contributing to delirium were addressed and therefore provides a truer test of the efficacy of donepezil therapy.

Randomization—All consenting subjects were randomized to donepezil treatment vs. placebo using a permuted block scheme. Because of the importance of dementia in delirium incidence, persistence, and recovery, the randomization scheme stratified on dementia, as assessed from the medical record and by the Informant Questionnaire for Cognitive Decline (IQCODE) (14), obtained from the proxy as part of the intake assessment. This stratified design also controlled for any effect donepezil might have on underlying dementia rather than on delirium.

Treatment—The medical center's research pharmacy dispensed active drug and placebo. Patients, providers, and the study team were all masked to treatment assignment, which could be unmasked only on a “need to know” basis after principal investigator approval; in this case, study interviewers remained masked until recruitment ended. Because we performed this study independent of pharmaceutical sponsorship, the research pharmacy placed donepezil 5 mg tablets into capsules, and also prepared matching capsules filled with placebo. We aimed to initiate the study drug on the day before surgery, or when this was not possible, within 24 hours after surgery. The study drug was administered daily, unless adverse events supervened, for a total treatment course of 30 days. We maintained a 5 mg/day dose of donepezil throughout the duration of the trial. This dose is sufficient to block 65–70% of red blood cell acetylcholinesterase (15), and we felt a rapid increase in dose to 10 mg would be likely to result in a much higher incidence of side effects (15).

Post-discharge treatment—When a study participant was discharged from the hospital, the remaining 30-day supply of “study drug” was sent with the subject for administration by the post-acute facility or by the family if the patient returned to the community. Because the majority of subjects were transferred to post-acute facilities for rehabilitation during the 30-day treatment period, we closely coordinated medication management with these facilities. An informational packet describing the study protocol, and a copy of the informed consent were provided to the post-acute facility at the time of the subject's hospital discharge. The study coordinator also personally contacted post-acute providers to ensure continuity of study drug treatment. This was verified by review of the post-acute nursing medication administration record during follow-up patient interviews.

Ongoing drug adherence and safety monitoring—During the 30-day treatment period, all enrolled subjects underwent regular adherence and safety reviews by the study coordinator on each postoperative day while in the hospital, and at 1,2,3, 4, and 6 weeks after discharge. For adherence, the nurse at the hospital or post-acute facility and the caregiver in the community counted the capsules remaining in the standardized pill dispenser, and this was cross-referenced with the initiation date of therapy to ensure that capsules were being taken on a daily basis. We also conducted standardized monitoring for adverse drug effects that included direct patient interviews, interviews with the patient's primary nurse or caregiver, and review of the medical record. All adverse drug effects and drug withdrawals were recorded and reviewed.

Data Safety and Monitoring Board (DSMB)—Two experts in the area of delirium and hip fracture management reviewed all study procedures before initiation of the trial, and decided on appropriate adverse event monitoring. After initiation of the study, the DSMB convened every 3 months to review all adverse events and reviewed serious adverse events in a “real time” fashion. DSMB recommendations for improved trial conduct and safety were implemented immediately.

Data collection protocol

Intake assessment—All consenting participants underwent an intake assessment that included a structured delirium assessment (16). We also interviewed the patient's primary caregiver with the (IQCODE) to assess the presence of pre-fracture dementia (14), the modified Katz Activities of Daily Living (17) to assess pre-fracture functional status, and also ascertained the patient's highest educational attainment.

Delirium assessment—Delirium was assessed masked to treatment status using an established, reliable protocol performed by a trained research interviewer (16). The interview consists of the Folstein Mini-Mental State (MMSE), a brief interview to assess overall cognitive functioning (18); Digit Span for supplemental attentional testing (19); the Delirium Symptom Interview (DSI), a validated interview designed to elicit 8 key symptoms of delirium (20). Data from these interviews were used to complete the Memorial Delirium Assessment Scale (MDAS), a 0–30 scale that measures the severity of delirium symptoms (21) and the Confusion Assessment Method (CAM) (22), a widely-used validated algorithm that determines the presence or absence of delirium.

Follow-up assessments—All subjects were re-evaluated on each postoperative hospital day, and at 2, 4, and 6 weeks after enrollment by a trained research interviewer. At each time point, the validated structured delirium assessment described above was repeated (16). We have previously shown that week 2 is a crucial time point for assessing resolution of delirium and functional recovery (23). Week 4 was chosen to coincide with the end of active treatment, and week 6 was chosen to assess delirium symptoms two weeks after discontinuation of treatment. Importantly, follow-up interviews were conducted regardless of patient location, whether in the hospital, rehabilitation facility, or home setting.

Outcome Measures, Data Analysis, and Sample Size Considerations

Outcome Measures—The primary study outcome measure was the presence delirium over time, defined using the CAM (22). The secondary outcome was delirium symptoms, measured using the MDAS (21). We included the MDAS as an outcome measure because it is continuous, and therefore more likely to be responsive to change over time than the CAM.

Data Analysis—All analyses were performed using standard randomized trial methods, including intention-to-treat analyses (24). First, we described study enrollment and retention

using a CONSORT diagram. We then present baseline characteristics in the active treatment and placebo arms. We then assessed drug safety and tolerability by comparing rates of side effects, adverse events, and drug withdrawal in the active treatment and placebo arms. Finally, we compared our two outcome measures, CAM-defined delirium and MDAS-defined delirium symptoms in the two arms over time. Outcome measures were compared using univariate methods (chi-square tests and Wilcoxon rank sum tests) and repeated measures time-dependent multivariable analyses using Generalized Estimating Equations (25). All analyses were performed using the SAS Statistical package, version 9.13 (Cary, N.C.).

Sample size considerations—Since this was a pilot trial, we did not target our sample size to achieve statistically significant results. Rather, we wanted to assess: 1) subject accrual for the trial, 2) drug tolerability and safety, and 3) effect size estimates for drug treatment effects. If our results were favorable, we would proceed with a definite Phase III clinical trial.

RESULTS

Subject Accrual

We actively screened and enrolled participants from January 2007 until August 2008. During this time period, a total of 93 eligible hip fracture patients were admitted to the medical center, of which 60 (65%) were approached for participation. The primary reason for non-approach was unavailability of study staff during weekend and holiday periods. Of the 60 patients approached, 16 (27%) patients provided informed consent and were enrolled in the study. This is substantially lower than the 50% anticipated enrollment rate. Among the 44 patients who refused participation, the primary reasons cited were: 1) unwillingness to add an additional medication to already complex drug regimens (N=14), 2) unwillingness to incur the added burden of participating in this trial (N=7), 3) unwillingness to participate in research in general (N=5), 4) specific concerns around donepezil side effects (N=4), 5) inability to contact caregiver when patient lacked capacity for consent (N=3), and 6) other reasons (N=11). The subject screening, eligibility, enrollment, and follow-up experience is summarized in Figure 1 (CONSORT diagram).

Baseline characteristics

Baseline characteristics of the participants in the donepezil and placebo arms are presented in Table 1. This was a very elderly sample with mean age of over 87 years old. Given the small sample size, most of the characteristics of the two treatment arms were reasonably well balanced, although the donepezil group had a higher proportion of women. Notably, the prevalence of dementia was nearly identical, demonstrating that our stratified randomization was effective.

Drug adherence, tolerability, and safety

Information on drug adherence, safety, and tolerability is presented in Table 2. Overall, drug adherence was quite good, with median percent of pills taken per days on protocol over 90% in both treatment arms. Comparison of side effects, which were ascertained in a masked fashion, suggests substantial imbalance with participants in the donepezil arm experiencing more side effects. In particular, there was substantially more insomnia and diarrhea in the active treatment arm; these are both known side effects of donepezil. In summary, 100% of the donepezil treated participants experienced at least one side effect, compared to 44% of those in the placebo arm ($p=0.04$).

There were no significant differences in the rates of Serious Adverse Events (SAEs) or Code Breaking Events in the two treatment arms, though in both cases all such events occurred in the donepezil group. It should be noted that both SAEs were prospectively classified as unlikely related to study participation. Taken in sum, our drug tolerability and safety results suggest that donepezil was not particularly well tolerated in our very elderly hip fracture sample.

Effects of Donepezil on Delirium Presence and Severity over Time

The effects of donepezil on the principal study outcomes—delirium presence and severity—are presented in Table 3. While the numbers are small, there are no substantial trends toward reduced presence or severity of delirium in the donepezil arm at any of the time points examined. In addition, repeated measures regression for both outcomes did not demonstrate clinically significant effects of donepezil. Analyses stratified by delirium presence at the time of drug initiation did not demonstrate effect modification by whether donepezil was used for delirium prevention or treatment.

DISCUSSION

Enrollment in our pilot trial was significantly worse than anticipated, with high ineligibility rates (nearly 2/3), and low enrollment rates (27%). Many patients and proxies were unwilling to participate in the trial as they wanted to minimize exposure to new medications. Our side effect and safety monitoring data suggest that donepezil is associated with a significantly higher frequency of side effects, and the two serious adverse events in the trial occurred in the donepezil arm. Finally, there is little evidence of benefit from donepezil in terms of reduction of delirium symptoms or duration. In sum, our data suggest that a definitive Phase III trial of donepezil for the prevention or treatment of delirium in hip fracture patients is not warranted.

Our results are consistent with several recent studies, which showed no benefit of donepezil for the prevention or treatment of postoperative delirium. Two of the largest of such studies were performed in elective orthopedic populations (11, 12). This enabled the investigators to initiate treatment several weeks before the surgical procedure, which we were unable to do given the emergency nature of hip fracture repair. One trial found no effect of donepezil on the incidence of postoperative delirium (11), while the other found a non-significant trend toward a protective effect (12). Another small trial published in abstract form only examined donepezil in a mixed elective and emergency orthopedic population, and reported results very similar to ours—substantial difficulties with enrollment (26) and no benefit of donepezil on delirium outcomes (27). None of these trials raised issues with drug tolerability or safety. However, just this year, a randomized trial using the related cholinesterase inhibitor rivastigmine for treatment of delirium in the intensive care unit (ICU) was terminated early due to an excess of deaths in the active treatment arm (28). A Cochrane review published in 2008 stated “there is currently no evidence supporting the use of donepezil for the management of delirium” (13).

The apparent lack of benefit of donepezil for delirium is disappointing, particularly since the “cholinergic deficiency hypothesis” is one of the leading pathophysiological models for delirium (10). While there is substantial evidence supporting this model, including reports of elevated levels of serum anticholinergic activity in patients with delirium (29, 30), it may not pertain in all clinical situations. Hip fracture patients receive multiple medications, including those with anticholinergic side effects, but they have multiple other acute stressors contributing to delirium, such as pain, inflammatory insults, and general anesthesia. Even if cholinergic deficiency is the primary mechanism for delirium in these patients, donepezil

and related drugs, which often take weeks for full effect in dementia (15), may not be able to reverse this deficiency in the time frame necessary to have an impact on delirium.

Perhaps more concerning is the side effect and safety profile of cholinesterase inhibitors used in the acute setting. For the most part, these drugs have a good safety record when used in dementia patients in the chronic setting (9, 15), though some patients are unable to tolerate the 10 mg dose due to pro-cholinergic side effects. The acute setting experienced by hip fracture and ICU patients involves a much more dynamic situation with hemodynamic fluxes and multiple drug initiations and interactions. These are generally not present in chronic outpatient use of these cholinesterase inhibitors in dementia patients. Recent data (28), including ours, raise questions about the safety of cholinesterase inhibitors initiated in the acute setting.

Our results should be interpreted in light of our study's strengths and limitations. By far the greatest limitation is the small sample size. We also recruited a small percentage of the eligible population. On the other hand, we enrolled a very elderly population (average age in high 80's), which would be the population at greatest risk for delirium after hip fracture. These weaknesses are balanced by our trial's strengths, which include most importantly, prospective, rigorous, and masked ascertainment of all study outcomes, including treatment side effects and delirium outcomes. In addition, our stratified randomization scheme achieved balance of pre-fracture dementia status. Finally, despite the small sample size, we found significant differences in the side effects experienced in the two treatment arms, favoring the placebo. Overall, we believe the study's strengths outweigh the weaknesses, and our study represents a valuable addition to the relatively limited literature on this topic.

In conclusion, our pilot trial of donepezil for the management of delirium in hip fracture patients did not demonstrate favorable treatment effects with regard to delirium presence or severity over time. Our study did find significantly more side effects in the active treatment arm, particularly increased insomnia and diarrhea. Enrollment in our trial was difficult, and most eligible patients and their proxies refused participation. Overall, we did not find sufficient evidence from our pilot to warrant a definitive Phase III trial. Trials of alternative treatment strategies for delirium, and a better understanding of the pathophysiology of this complex syndrome, are needed to move the field forward.

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Figure 1.
CONSORT Diagram for the Trial

Table 1

Baseline Characteristics of the Treatment Arms

Characteristic	Donepezil (N = 7)	Placebo (N = 9)
Participant Age (Mean $\pm$ STD, yrs)	88.0 $\pm$ 5.2	87.0 $\pm$ 3.7
Participant Gender – Female N(%)	5 (71%)	4 (44%)
Participant Race		
Black N(%)	1 (14%)	1 (11%)
White N(%)	6 (86%)	8 (89%)
Participant H/O Dementia		
Yes N(%)	3 (43%)	4 (44%)
No N(%)	4 (57%)	5 (56%)
Pre-fracture ADL Score (Mean $\pm$ STD) (0– 16, 16 best)	13.3 $\pm$ 3.6	12.8 $\pm$ 4.7
Participant Education		
< High School N(%)	0	0
High School N(%)	1 (14%)	3 (33%)
Some College N(%)	2 (29%)	2 (22%)
Associate Degree N(%)	1 (15%)	0
Bacc Degree N(%)	1 (14%)	1 (11%)
Masters N(%)	1 (17%)	1 (11%)
Doctoral N(%)	0	1 (11%)
Unknown N(%)	0	1 (11%)
Anticholinergic Drug Exposure		
Preoperative	1 (14%)	0
Postoperative	7 (100%)	7 (78%)
Neuroleptic Drug Exposure		
Preoperative	2 (29%)	1 (11%)
Postoperative	3 (43%)	4 (44%)

Per the CONSORT recommendations for the reporting of clinical trials (24), no p-values are included in this table.

Table 2
Drug Adherence, Tolerability, and Safety

Characteristic	Donepezil (N = 7)	Placebo (N = 9)	p-value
Drug Adherence % Pills Taken/Days on Protocol Median (min, max)	94% (17%, 97%)	97% (7%, 100%)	0.2 [#]
Side Effects:			
Insomnia	5/7=71%	1/9=11%	0.04
Diarrhea	3/7=43%	0/9	0.06
Nausea	2/7=29%	2/9=22%	1.0
Vomiting	1/7=14%	1/9=11%	1.0
Syncope	1/7=14%	0/9	0.4
Dizziness	0/7	1/9=11%	1.0
Anorexia	0/7	1/9=11%	1.0
Frequency of Urination	1/7=14%	0/9	0.4
Total Side Effects per Patient Median (min, max)	2 (1, 3)	0 (0, 3)	0.02 [#]
Any Side Effects	7/7=100%	4/9=44%	0.04
Serious Adverse Events *			
Total Number of Events Observed	N=2	N=0	
Number of Patients with SAE (%)	2/7=29%	0/9	0.2
Code Breaking Event †			
Total N	N=2	N=0	0.2
Drug Stopped Early N (%)	2 (29%)	3 (33%)	1.0

* All serious adverse events were reviewed prospectively and reported to the IRB. All were deemed unlikely related to study participation.

† Code breaking event occurred when either the study team or the clinical staff requested drug unmasking due to a clinical situation.

[#] P-values for drug adherence and side effects per patient are based on Wilcoxon rank sum tests. All other p-values are based on Fisher exact tests.

Table 3A

Effect of Donepezil on Delirium Presence over time based on the CAM*

	Donepezil (n = 7)	Placebo (n = 9)	p value [†]
Pre-randomization	1/7 (14%)	4/9 (44%)	--
Hospital Interviews (more than one per subject)	7/11 (64%)	9/14 (64%)	0.9
Week 2	3/7 (43%)	3/7 (43%)	1.0
Week 4	1/6 (17%)	3/7 (43%)	0.6
Week 6	3/6 (50%)	3/6 (50%)	1.0

* Confusion Assessment Method (CAM) - Measure of the presence or absence of delirium. Requires: 1) Acute change with fluctuating course, 2) inattention, and either 3) disorganized thinking or 4) altered level of consciousness

[†] P value derived from the Fisher's Exact Test

Overall effect of donepezil on delirium presence over time using a repeated measures logistic regression model from Generalized Estimating Equations: Odds ratio=0.9, 95% Confidence Intervals: [0.4, 2.3].

Table 3B

Effect of Donepezil on Delirium Severity over time based on the MDAS*

	Donepezil (n = 7)	Placebo (n = 9)	p value [†]
Pre-randomization [#]	Score 6.3 ± 3.4	Score 8.4 ± 6.5	0.6
Hospital Discharge [#]	1.3 ± 2.5	1.6 ± 5.2	0.9
Week 2 [#]	-0.1 ± 2.3	-2.2 ± 4.9	0.6
Week 4 [#]	-1.2 ± 3.5	-2.0 ± 6.4	0.6
Week 6 [#]	-0.6 ± 2.6	-2.0 ± 7.5	1.0

* Memorial Delirium Assessment Scale (MDAS): Measures the severity of 10 delirium symptoms items scored 0–3 (0 is not present; 1 is mild; 2 is moderate; 3 is severe) yielding a total score of 0–30 with 30 most severe

[†] Due to the non-normal nature of the data, p values are derived from a Wilcoxon rank sum test.

[#] At Pre-randomization, we report the total MDAS score. At hospital discharge and weeks 2, 4, and 6, we report change from pre-randomization MDAS score.

Overall effect of donepezil on delirium symptoms over time using a repeated measures linear regression model from Generalized Estimating Equations adjusted for pre-randomization MDAS score: effect size -0.2 on 30 point MDAS scale, 95% Confidence Intervals: [-1.5, 1.2].