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A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS

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ABSTRACT

Background Since in hospitalized older patients delirium is associated with poor outcomes, we evaluated the effectiveness of a multicomponent strategy for the prevention of delirium.

Methods We studied 852 patients 70 years of age or older who had been admitted to the general-medicine service at a teaching hospital. Patients from one intervention unit and two usual-care units were enrolled by means of a prospective matching strategy. The intervention consisted of standardized protocols for the management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Delirium, the primary outcome, was assessed daily until discharge.

Results Delirium developed in 9.9 percent of the intervention group, as compared with 15.0 percent of the usual-care group (matched odds ratio, 0.60; 95 percent confidence interval, 0.39 to 0.92). The total number of days with delirium (105 vs. 161, P=0.02) and the total number of episodes (62 vs. 90, P=0.03) were significantly lower in the intervention group. However, the severity of delirium and recurrence rates were not significantly different. The overall rate of adherence to the intervention was 87 percent, and the total number of targeted risk factors per patient was significantly reduced. Intervention was associated with significant improvement in the degree of cognitive impairment among patients with cognitive impairment at admission and with a significant reduction in the rate of use of sleep medications among all patients. Among the other risk factors, there were trends toward improvement in immobility, visual impairment, and hearing impairment.

Conclusions The risk-factor intervention strategy that we studied resulted in significant reductions in the number and duration of episodes of delirium in hospitalized older patients. The intervention had no significant effect on the severity of delirium or on recurrence rates; this finding suggests that primary prevention of delirium is probably the most effective treatment strategy. (N Engl J Med 1999;340:669-76.)

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(i.e., the presence of predisposing conditions, such as cognitive impairment, severe illness, or visual impairment) and hospital-related insults (i.e., medications and procedures). The risk of delirium increases with the number of risk factors present.

Therefore, a multicomponent approach targeted to the patient’s risk factors is the most clinically relevant and potentially effective intervention for delirium.

We conducted a controlled clinical trial of a multicomponent strategy to reduce the number of risk factors for delirium with the goal of preventing delirium in hospitalized older patients. Our aims were to compare the effectiveness of a multicomponent strategy for reducing the risk of delirium with that of a usual plan of care for hospitalized older patients, to determine the level of adherence to the intervention protocol, and to measure the effect of the intervention on the targeted risk factors.

METHODS

Study Design

This controlled clinical trial used prospective, individual matching to compare patients admitted to one intervention and two usual-care (control) units at a teaching hospital. Random assignment of subjects to the intervention or usual-care units was not possible because of the large number of patients in all medical units during the time of the study. A pilot study confirmed that randomization was not feasible, because beds in the units intended for study were often unavailable.

The prospective, individual matching strategy was chosen as an alternative to randomization that would ensure that patients in our study groups were comparable at base line. This strategy has been described in detail previously. In brief, all the subjects in the intervention unit who met the eligibility criteria were enrolled. Concurrently, eligible patients from two usual-care units were identified, so that the subject pool was sufficiently large to permit the use of a computerized algorithm designed to match patients according to age within five years, sex, and base-line risk of delirium (intermediate or high) as defined by our previously developed predictive model. The predictive model included four of the risk factors for delirium: visual impairment, severe illness, cognitive impairment, and a high ratio of blood urea nitrogen to creatinine. Intermediate risk was defined as the presence of one or two risk factors at base line, and high risk as the presence of three or four risk factors at base line. The matching factors were selected because previous work had established them as important predictors of the development of delirium. To control for changing patterns of care over time, patients in the intervention group and matched usual-care patients were required to have been admitted within 180 days of each other. The computerized algorithm matched patients prospectively, strictly on the basis of their characteristics at admission.

Setting and Patients

Potential participants in the study were consecutive patients admitted to the general-medicine service (non-intensive care) at Yale-New Haven Hospital from March 28, 1995, through March 28, 1997. Yale-New Haven Hospital, an 800-bed urban teaching hospital with 200 medical beds, serves a large number of patients from the community as well as a population of referred patients. A total of 2434 patients were potentially eligible to participate: they were admitted to one of three general-medicine units, were at least 70 years old, had no delirium at the time of admission, and were intermediate or high risk for delirium at base line. Of these, 1265 patients were excluded because of inability to participate in interviews (because of profound dementia that precluded verbal communication [154 patients], a language barrier [92], profound aphasia [38], or intubation or respiratory isolation [14]), coma or terminal illness (69 patients), a hospital stay of 48 hours or less (219), prior enrollment in this study (324), or other reasons (e.g., unavailability of an interviewer or unavailability of the patient because of examinations or procedures elsewhere in the hospital) (355). Of the remaining 1169 eligible patients, the patient, family, or physician refused enrollment in 250 cases and a matching patient could not be found in 67 cases. Thus, the final study sample included 852 patients, who were matched as 426 pairs of patients receiving the study intervention and usual care.

The 1265 patients who were excluded did not differ significantly from the 852 patients who were enrolled in terms of age, sex, or base-line risk of delirium; however, a larger proportion of patients receiving usual care were excluded (63 percent vs. 50 percent in the intervention group; P = 0.001), mainly because more patients were available for screening in the two usual-care units. The 250 patients who declined to participate did not differ significantly from the 852 who enrolled in terms of age, sex, baseline risk of delirium, or group assignment. Of the 919 qualified patients who agreed to enroll, 67 (7 percent) could not be matched (24 in the intervention group and 43 in the usual-care group). These 67 unmatched patients, as compared with the 852 enrolled patients, were significantly older (mean age, 84 and 80 years, respectively), had a higher risk of delirium at base line (high risk, 42 percent vs. 28 percent), and were more likely to be admitted to a usual-care unit (64 percent vs. 50 percent). These differences were due to the inherent difficulty of finding matches for patients who were at extreme ends of the matching criteria (e.g., extremely old); patients receiving usual care predominated because of the matching algorithm, which kept a pool of unmatched patients receiving usual care available to facilitate subsequent matching.

Informed consent for participation was obtained orally from the patients or, for those with substantial cognitive impairment, from a proxy (usually the closest relative), according to procedures approved by the institutional review board of the Yale University School of Medicine.

Assessments

All the assessments were carried out by members of a research staff who had no role in the intervention and who were unaware of the nature of the study and of the patients’ group assignment. The staff was composed of research nurses and experienced clinical researchers, all of whom underwent intensive training and followed standard procedures outlined in a detailed training and coding manual. At base line, standardization of assessments and measurements of interrater reliability verified the consistency of ratings among all the staff members. Subsequently, researchers met monthly to review procedural and coding issues. Quality checks of interviews and assessments of the interrater reliability with respect to the primary outcomes and targeted risk factors were performed every six months. All the data were collected on standardized, precoded forms, and the data were entered twice into a computerized data base and underwent extensive checks of error and validity.

The screening interview included the Mini–Mental State Examination, the Digit Span Test, evaluation by the Confusion Assessment Method, assessment of Katz’s Activities of Daily Living, the standard Jaeger test for vision, and chart review to determine the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) score. The Mini–Mental State Examination measures cognitive functioning on a scale of 0 (poor) to 30 (excellent), with a score of less than 24 indicating cognitive impairment. The orientation score consists of the 10 orientation items on the Mini–Mental State Examination, each scored on a scale of 0 to 10, with lower scores indicating inattention. Evaluation of Katz’s
Activities of Daily Living assess the ability to perform seven basic-care skills (feeding, bathing, grooming, dressing, using the toilet, transferring between bed and chair, and walking) on a scale of 0 to 14, with lower scores indicating functional impairment.

Eligible patients then underwent the base-line assessment, which included the collection of demographic data, assessment of instrumental activities of daily living, the Whisper Test for hearing, and assessment of sleep. Visual impairment was defined as binocular near vision, after correction, worse than 20/70 as measured by the standard Jaeger test. The APACHE II score measures severity of illness on a scale of 0 to 71, with higher scores indicating increased severity. The instrumental Activities of Daily Living scale assess the ability to perform seven complex activities (using the telephone, grocery shopping, using transportation, cooking, housekeeping, taking medications, and handling finances) on a scale of 0 to 14, with lower scores indicating functional impairment. The Whisper Test measures hearing according to the number of 12 whispers heard, with 6 or fewer indicating hearing impairment. A family member was interviewed at the time of admission and asked to describe the patient’s cognitive functioning before admission and any recent cognitive changes and to complete the modified Blessed Dementia Rating Scale, an observer-rated score that correlates directly with the number of neuritic plaques found on postmortem examination of the brain. The modified (shortened) version has been tested of possible dementia. A ratio of blood urea nitrogen to creatinine (both measured in milligrams per deciliter) of 18 or greater indicates possible dementia. A ratio of blood urea nitrogen to creatinine (both measured in milligrams per deciliter) of 18 or greater was used as an index of dehydration. Screening and base-line assessments were completed within 48 hours after admission.

Subsequently, patients were evaluated daily until discharge with a structured interview consisting of the Digit Span Test, Mini–Mental State Examination, and Confusion Assessment Method rating. On hospital day 5 or at discharge (if discharge was before day 5), patients were reassessed for risk factors for delirium (Table 1). After discharge, medical records were reviewed for evidence of delirium, final diagnoses, medications, laboratory results, and destination after discharge.

**Intervention**

The intervention strategy, called the Elder Life Program, was implemented by a trained interdisciplinary team, which consisted of a geriatric nurse-specialist, two specially trained Elder Life specialists, a certified therapeutic-recreation specialist, a physical-therapy consultant, a geriatrician, and trained volunteers. The performance of each staff member, including volunteers, was evaluated quarterly, with completion of checklists to ensure competency and consistent and complete adherence to all intervention protocols.

Six risk factors for delirium were targeted for intervention: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. These factors were selected on the basis of evidence of their association with the risk of delirium and because they were amenable to intervention strategies considered feasible in the context of current hospital practice. Table 1 describes the risk group that received each intervention, the standardized intervention protocols for each risk factor, and the targeted outcome for each intervention protocol.

**Usual Care**

Usual care consisted of standard hospital services provided by physicians, nurses, and support staff (e.g., physical therapists, pharmacists, and nutritionists) in the other general-medicine units. Members of the intervention team did not provide services

<table>
<thead>
<tr>
<th>Targeted Risk Factor and Eligible Patients</th>
<th>Standardized Intervention Protocols</th>
<th>Targeted Outcome for Reassessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment*</td>
<td>Orientation protocol: board with names of care-team members and day’s schedule; communication to resident and towards of cognizance. Therapeutic-activities protocol: cognitively stimulating activities three times daily (e.g., discussion of current events, structured reminiscence, or word games).</td>
<td>Change in orientation score</td>
</tr>
<tr>
<td>Sleep deprivation</td>
<td>Nonpharmacologic sleep protocol: at bedtime, warm drink (milk or herbal tea), relaxation tapes or music, and back massage. Sleep-enhancement protocol: universal noise-reduction strategies (e.g., silent pill crushers, vibrating beepers, and quiet hallways) and schedule adjustments to allow sleep (e.g., rescheduling of medications and procedures).</td>
<td>Change in rate of use of sedative drug for sleep†</td>
</tr>
<tr>
<td>Immobility</td>
<td>Early-mobilization protocol: ambulation or active range-of-motion exercises three times daily; minimal use of immobilizing equipment (e.g., bladder catheters or physical restraints)</td>
<td>Change in Activities of Daily Living score</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>Vision protocol: visual aids (e.g., glasses or magnifying lenses) and adaptive equipment (e.g., large illuminated telephone keypads, large-print books, and fluorescent tape on call bell), with daily reinforcement of their use. Hearing protocol: portable amplifying devices, car wax, dissection of the brain, and special communication techniques, with daily reinforcement of these adaptations. Dehydration protocol: early recognition of dehydration and volume repletion (i.e., encouragement of oral intake of fluids).</td>
<td>Early correction of vision, ≤48 hr after admission</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>Hearing protocol: portable amplifying devices, car wax, dissection of the brain, and special communication techniques, with daily reinforcement of these adaptations. Dehydration protocol: early recognition of dehydration and volume repletion (i.e., encouragement of oral intake of fluids).</td>
<td>Change in Whisper Test score</td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td>Change in ratio of blood urea nitrogen to creatinine</td>
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</tbody>
</table>

*The orientation score consisted of results on the first 10 items on the Mini–Mental State Examination (MMSE).
†Sedative drugs included standard hypnotic agents, benzodiazepines, and antihistamines, used as needed for sleep.
to patients assigned to usual care. However, the same attending and resident physicians provided care to patients in both study groups.

Outcomes

The primary outcome was delirium, defined according to the Confusion Assessment Method criteria, which consisted of acute onset and a fluctuating course of symptoms of delirium, inattention, and either disorganized thinking or an altered level of consciousness. Each of these features was rated by the researchers on the basis of observations made during the daily interviews. The Confusion Assessment Method criteria provided a standardized rating of delirium, which has been validated against geropsychiatric diagnoses, with a sensitivity of 94 to 100 percent, a specificity of 90 to 95 percent, and high interobserver reliability.

For the primary analysis of the effectiveness of the intervention, delirium was considered a binary outcome (present or absent) according to its earliest occurrence, and only one episode of delirium per patient was counted. We also counted the total number of days of delirium (the total person-days of all episodes of delirium) and the number of episodes of delirium in each study group, and we evaluated recurrence (two or more episodes) and severity. The severity of delirium was measured by an additive score for the four designated symptoms (symptom fluctuation, inattention, disorganized thinking, and an altered level of consciousness). Each symptom of delirium except fluctuation was rated as absent, mild (1 point), or marked (2 points); symptom fluctuation was rated as absent (0 points) or present (1 point). The sum of these ratings yielded a delirium-severity score, ranging from 0 to 7, with higher scores indicating increased severity.

Confusion Assessment Method ratings were completed in 4848 of 4857 daily interviews (99.8 percent). Interrater reliability for these ratings was confirmed in 16 paired observations that involved all the members of the research staff (kappa, 1.0). A total of 108 uncertain ratings, ratings with missing Confusion Assessment Method items, or possible episodes of delirium occurring between interviews were assessed for the presence or absence of delirium by two independent reviewers (a geriatrician and a neuropsychologist who were unaware of the patients’ study-group assignments) on review of all interview data and medical records.

Adherence

The level of adherence to the intervention, with reasons for nonadherence, was recorded daily by the intervention staff. Daily adherence was complete if the patient received all parts of the assigned protocol for the total number of times it was to be given. Partial adherence indicated that the patient either received some but not all parts of the protocol or did not receive the protocol for the required number of times that day. Nonadherence indicated that none of the parts of the assigned protocol were received that day.

Statistical Analysis

Characteristics at admission were compared between patients within matched pairs by matched statistical analyses, either paired t-tests for continuous variables or McNemar’s test for binary measures. These results were confirmed with unmatched analyses.

All analyses of the effectiveness of the intervention with regard to the primary outcome used the intention-to-treat approach. The effectiveness of the intervention strategy in reducing the incidence of delirium was evaluated by a method of conditional logistic regression developed by Holford et al. for prospectively sampled, individually matched data. To identify potential confounders, all the base-line characteristics were examined in bivariate analyses, and factors associated at a level of P=0.20 with the type of treatment (intervention or usual care) were further examined. Each potential covariate was added individually to the model and was retained if its presence resulted in a modification of the log-linear parameter for an intervention effect of 10 percent or more. Subsequently, unmatched analyses by means of traditional logistic regression for new cases of delirium during the hospital stay and Cox proportional-hazards analysis for the risk of delirium per hospital day, with adjustment for the matching factors, were carried out to provide comparisons and alternatives to the matched analyses, as advocated by previous investigators.

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RESULTS

The characteristics of the patients in each study group at the time of admission are shown in Table 2. The intervention and usual-care groups did not differ significantly in terms of any of the characteristics. Many patients with dementia were included in the study; scores on the Mini–Mental State Examination ranged from 7 to 30, with 25 percent of the patients having a score of 20 or less. The mean numbers of risk factors per patient at admission were similar in the two groups. The median lengths of stay were 7.0 and 6.5 days in the intervention and usual-care groups, respectively (P=0.95). Six patients in the intervention group (1.4 percent) and seven in the usual-care group (1.6 percent) died during hospitalization (P=0.78); complete information on delirium was available for these subjects.

Overall Effectiveness

The rate of incidence of delirium was significantly lower in the intervention group than in the usual-care group (9.9 percent vs. 15.0 percent, P=0.02). The matched odds ratio of 0.60 (95 percent confidence interval, 0.39 to 0.92) in matched multivariable analyses indicates that a substantial reduction in risk was associated with the intervention (Table 3). After examination of all the potential base-line covariates (Table 2), only a Mini–Mental State Examination score of less than 24 was significantly associated with outcome (P<0.01). Adjustment for the score, however, did not substantially affect the overall results, and thus we did not control for this variable in subsequent models. Unmatched multivariable analyses, including both logistic-regression and Cox proportional-hazards analyses, with adjustment for matching factors, confirmed the matched results. The cumulative incidence of delirium was significantly lower in the intervention group than in the usual-care group (Fig. 1).

The total number of days of delirium was significantly lower in the intervention group than in the
The cumulative incidence of delirium was defined as the probability of the development of delirium by a specified time. Data on patients were censored at the time of discharge or death. The difference between the groups was significant (chi-square = 4.77; P=0.03 by the log-rank test). Kaplan–Meier estimates of the incidence of delirium at the median length of the hospital stay (seven days, indicated by the dotted line) were 0.100 for the intervention group and 0.145 for the usual-care group.

**Effect on Targeted Risk Factors**

The change in risk factors or targeted outcomes at the reassessment on day 5 or at discharge is shown in Table 4. At reassessment, there was significant improvement in the orientation score and a significant reduction in the rate of use of sedative drugs for sleep in the intervention group as compared with the usual-care group. The Activities of Daily Living score and the score on the Whisper Test demonstrated trends toward improvement in the intervention group. Receipt of early vision correction was also associated with a trend toward improvement in this group. Overall, there were significantly fewer risk factors present in the intervention group than in the usual-care group at reassessment.

**Cost of Intervention**

The total cost of the intervention, including staff time spent in intervention activities, equipment, supplies, and consultant costs, was $139,506, or an average of $327 per patient in the intervention group. The cost of intervention per case of delirium prevented was $6,341 ($139,506 for 22 cases prevented [64 cases of delirium occurred in patients receiving usual care, as compared with 42 cases in those receiving the intervention]).

**DISCUSSION**

This controlled clinical trial provides evidence that a multicomponent, targeted intervention strategy, the Elder Life Program, is effective for the prevention of delirium in hospitalized older medical patients. The intervention prevented the initial development of delirium and reduced the total number of days of delirium. It was most effective in patients who were at intermediate risk for delirium at baseline. Once an initial episode of delirium had occurred, however, the intervention had no significant effect on the severity of delirium or on the likelihood of recurrence. This finding has an important implication for the treatment of delirium: primary prevention is probably the most effective strategy. Once delirium has occurred, our intervention strategy will be less effective and less efficient.

The strengths of this study include the daily assessment of patients for delirium with a standardized, validated instrument; the completeness of the
outcome data, with no losses to follow-up; the targeting of at-risk patients for intervention, an approach that maximizes the efficiency and clinical relevance of the intervention; and the detailed tracking of adherence to the intervention protocols. Moreover, the practical, realistic nature of the intervention protocols, designed to target well-documented risk factors for delirium, enhances their feasibility and the extent to which they can be applied in other settings.

These findings lend strong support to the use of a multicomponent intervention to prevent delirium. The positive trends in the reduction of risk factors at the time of reassessment validate the effectiveness of each intervention protocol. The significant reduction in the total number of risk factors with intervention as compared with usual care suggests that risk-factor reduction contributed at least in part to the effectiveness of the intervention strategy.

Several important limitations of this study deserve comment. Logistic constraints precluded random assignment of the patients to the two treatment groups. However, the prospective, individual-matching strategy allowed balanced assignment of the patients to the two groups. Furthermore, a contamination effect in the usual-care group probably decreased the overall rates of delirium. Contamination was evident in the rates of delirium, which were substantially lower than anticipated on the basis of earlier studies in the same study population.\textsuperscript{24,25} and it was also evident in the substantial reduction in risk factors that occurred in the usual-care group. Although efforts were made to avoid contamination, some intervention protocols were disseminated by word of mouth to staff members in usual-care units. Moreover, although the intervention strategies most often involved the nursing staff, the physicians rotated on all hospital floors and carried over some intervention protocols to the usual-care group. Despite these contamination effects, which would have tended to bias the results toward the null hypothesis, the significant overall results substantiate the robustness of the effects of the intervention.

The estimated cost of $6,341 per case of delirium prevented compares favorably with the estimated costs in other studies of $7,727 to $11,834 (in 1996 dollars) per fall prevented\textsuperscript{43} and $19,800 to $42,900 (in 1995 dollars) per myocardial infarction prevented.\textsuperscript{44} Although a formal cost-effectiveness analysis was beyond the scope of this study, a complete analysis of health care costs related to delirium may demonstrate that the intervention yields a net savings.

This trial holds substantial promise for the prevention of delirium in hospitalized older patients. Further evaluation is needed to determine the cost-effectiveness of the intervention; its effects on related outcomes, such as mortality, rehospitalization, institutionalization, use of home health care, and long-term cognitive functioning; and its effectiveness in other settings.

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