MASTER THESIS

THE EFFICACY OF HALOPERIDOL PROPHYLAXIS ON THE PREVENTION OF DELIRIUM IN GERIATRIC CARE

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December 2012

UNIVERSITY OF TWENTE.

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The efficacy of haloperidol on the prevention of delirium in geriatric care

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s0097454

18 December 2012

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Preface

With proud I present my master thesis to complete my master Health Sciences at the University of Twente.

After a year premaster courses of Health Sciences and half a year of master courses I was ready to start with my final assignment. Although it was not the assignment I originally signed up for, I started with great enthusiasm at Ziekenhuisgroep Twente. Unfortunately receiving access to the database Thinkwise did not go smoothly, which was a struggle for me. Time passed by and when I finally did get the access, it was hard to find motivation to continue with the assignment. When I finally did find my rhythm, I enjoyed the research, the analyses in SPSS and the writing.

I would like to thank Dr. Detlef van der Velde and Ellis Folbert for the opportunity to do this research for them. A special thanks to Ellis who was so kind to help me with the struggle of getting access to the database and the time she spend with me to discuss the content of my assignment, despite her busy schedule. I would also like to thank the secretary Liesbeth Becker – Elling who introduced me to Thinkwise and provided missing information by email.

I am really thankful for my supervisor Carine Doggen, who helped me through my master thesis in terms of content, but also as mental coach. Where my confidence was lacking, she made me see the positive aspects of my work. I always left with a positive feeling after a meeting. Also thanks to Jeannette van Manen for your input during the times we reviewed my work.

Finally I would like to thank my family and friends who were supportive during my graduation. From all of you I received feedback, peptalk, advice, laughter and relaxation which I really needed. To my fellow students I would like to say: thanks for the great time and your support!

Enschede, December 2012

Ingeborg Koning

Abstract

Introduction
Delirium is a common mental disorder which can lead to problems with consciousness, attention, memory, thought, behavior and orientation. Causes for a delirium can be a combination between a patients vulnerability and provoking factors during hospitalization. Risk factors for a delirium include age (above 65 years), dementia, co-morbidity, visual or hearing impairment, alcohol abuse, medication use and depression. Delirium is a serious problem for elderly hospitalized patients. The incidence of delirium for the elderly postoperative patient lies between 15% and 53%. The delirious patient has a longer length of hospital stay, higher mortality and morbidity rate and tends to have long-term cognitive impairment which is likely to reduce the quality of life. Prevention of delirium is therefore important. Haloperidol prophylaxis is an antipsychotic drug which is used for the prevention of delirium. Currently there are two Randomized Controlled Trials (RCTs) available about the efficacy of haloperidol prophylaxis on the prevention of delirium for elderly patients, which show conflicting results. Both RCTs have included different type of patients which could cause the different result in the efficacy of haloperidol prophylaxis on the incidence of delirium. Nonetheless, the Center for Geriatric Traumatology at Ziekenhuisgroep Twente questioned these results and changed their policy in which haloperidol prophylaxis was given as a preventive treatment for patients at risk for developing a delirium, in a policy where haloperidol prophylaxis was not given as a preventive treatment.

Research question
What is the efficacy of the treatment policy with or without haloperidol prophylaxis on the incidence of delirium, length of hospital stay, hospital mortality rate and complications that occur among patients aged 70 years and older with a fracture that visit the Center for Geriatric Traumatology (CGT) of Ziekenhuisgroep Twente (ZGT) for the first time? Similarly, the effect is assessed for patients treated with or without haloperidol prophylaxis.

Methods
This was a single center retrospective cohort study with a focus on two studies: a treatment policy study and a group study. Included were patients aged 70 years and older, with a fracture that entered the emergency ward at Ziekenhuisgroep Twente for the first time during the study period (March 18th 2008 till June 7th 2012) and were treated at the Center for Geriatric Care. In the treatment policy study, the treatment policy with haloperidol prophylaxis (March 18th 2008 – January 2012) was compared to the treatment policy without haloperidol prophylaxis (February 2012 – June 7th 2012). In the group study a group of patients treated with haloperidol prophylaxis was compared to a group of patients treated without haloperidol prophylaxis. Both studies were studied for all patients and hip surgery patients on the incidence of delirium, length of hospital stay, hospital mortality rate and complications that occur.

Results
In total 655 patients were included. The treatment policy with haloperidol prophylaxis consisted of 595 patients and the policy without haloperidol prophylaxis of 60 patients. The incidence of delirium for the policy with haloperidol prophylaxis was 24,0% versus 13,3% for the policy without haloperidol prophylaxis for all patients (RR = 1,80; 95% CI: 0,93 - 3,49). Adjustments for age and gender did not materially change this effect. In the policy with haloperidol prophylaxis for all patients a yearly decrease was found, with an incidence of delirium in 2011 of 14,5%. The incidence of delirium in 2011 compared to the incidence in 2012 resulted in a relative risk of 1,09 (95% CI: 0,50 – 2,40). The incidence of delirium for hip surgery patients of the policy with haloperidol prophylaxis was 30,6% versus 8,6% for the policy without haloperidol prophylaxis (RR = 3,57; 95% CI: 1,20 – 10,63). The crude odds ratio for the treatment policy with haloperidol prophylaxis compared to the treatment policy without haloperidol prophylaxis was 4,70 (95% CI: 1,41 – 15,64). After adjusting for gender and age the odds ratio changed to 5,12 (95% CI: 1,52 – 17,21). The length of hospital stay for all patients and hip surgery patients appeared to be longer for the policy with haloperidol prophylaxis compared to the policy

without haloperidol prophylaxis, with a mean difference of 1,5 days (95% CI: -1,7 – 4,6) and 2,9 days (95% CI: -1,2 – 6,9) respectively. The hospital mortality rate was 5,4% versus 0,0% (p=0,11) for all patients and 9,8% versus 0,0% (p =0,38) for hip surgery patients. The incidence of complications that occurred was 48,2% for the policy with haloperidol prophylaxis versus 46,7% for the policy without haloperidol prophylaxis for all patients (RR = 1,03; 95% CI: 0,78 – 1,37) and 57,4% versus 48,6% for hip surgery patients (RR = 1,18; 95% CI: 0,83 – 1,68).

The patient group with haloperidol prophylaxis consisted of 216 patients and the patient group without haloperidol prophylaxis of 439 patients. For the group with haloperidol prophylaxis the incidence of delirium was 51,9% versus 8,9% for the group without haloperidol prophylaxis for all patients (RR = 5,84; 95% CI: 4,21 – 8,09). The crude odds ratio was 11,05 (95% CI: 7,23 – 16,87). After adjusting for age and gender, the odds ratio changed to 9,36 (95% CI: 6,08 – 14,40). For hip surgery patients the incidence of delirium is 52,8% for the group with haloperidol prophylaxis versus 12,1% for the group without haloperidol prophylaxis (RR = 4,36; 95% CI: 3,05 – 6,24). The crude odds ratio was 8,12 (95% CI: 5,04 – 13,09) and after adjusting for age and gender the odds ratio changed to 7,06 (95% CI: 4,34 – 11,48). The mean difference in length of hospital stay was 2,0 days (95% CI: 0,1 – 4,0) for the group with haloperidol prophylaxis compared to the group without haloperidol prophylaxis for all patients. For hip surgery patients the mean difference was 1,8 days (95% CI: -0,4 – 4,1). The hospital mortality rate was for all patients 7,9% versus 3,4% (RR = 2,30; 95% CI: 1,17 – 4,52) and for hip surgery patients 7,9% versus 4,7% (RR = 1,68; 95% CI: 0,80 – 3,54). Complications that occur was for all patients 58,8% for the group with haloperidol prophylaxis versus 42,8% for the group without haloperidol prophylaxis (RR = 1,37; 95% CI: 1,18 – 1,60) and for hip surgery patients 62,9% versus 52,3% (RR = 1,20; 95% CI: 1,02 – 1,40).

Conclusion

The incidence of delirium appears to be higher for the treatment policy with haloperidol prophylaxis compared to the treatment policy without haloperidol prophylaxis for all patients and especially for hip surgery patients. The length of hospital stay appeared to be longer and the hospital mortality rate appeared to be higher for the treatment policy with haloperidol prophylaxis. The complications that occurred were higher for hip surgery patients in the treatment policy with haloperidol prophylaxis compared to the treatment policy without haloperidol prophylaxis.

The incidence of delirium for the patient group with haloperidol prophylaxis compared to the patient group without haloperidol prophylaxis was clearly different for all patients and hip surgery patients. A patient in the group with haloperidol prophylaxis had a higher risk of developing a delirium than a patient in the group without haloperidol prophylaxis. The length of hospital stay was longer and the hospital mortality rate was higher for all patients of the group with haloperidol prophylaxis. The incidence of complications was higher for all patients and hip surgery patients of the group with haloperidol prophylaxis compared to the group without haloperidol prophylaxis.

The efficacy of haloperidol prophylaxis on the prevention of delirium remains uncertain. The most important limitation of this study and its results, is the fact that only adjustments for the risk factor age and gender could be made. The other risk factors were not recorded, making it impossible to make adjustments for these factors. The results of this study should therefore be interpreted with care. Further research regarding the efficacy of haloperidol prophylaxis on the incidence of delirium is necessary.

Key words: *haloperidol prophylaxis, prevention, delirium, elderly, geriatric fracture center*

Samenvatting

Introductie
Delirium is een veel voorkomende psychische stoornis wat kan leiden tot problemen met bewustzijn, aandacht, geheugen, gedachten, gedrag en oriëntatie. Een delirium kan worden veroorzaakt door een combinatie van de kwetsbaarheid van een patiënt en uitlokkende factoren gedurende de ziekenhuis opname. Risico factoren voor het ontwikkelen van een delirium zijn leeftijd (ouder dan 65 jaar), dementie, comorbiditeit, visuele of auditieve beperkingen, alcohol- en medicatiegebruik en een depressie. Delirium is een serieus probleem voor oudere patiënten die zijn opgenomen in het ziekenhuis. De incidentie van delirium voor de oudere postoperatieve patiënt ligt tussen 15% en 53%. Een delirante patiënt verblijft langer in het ziekenhuis, heeft een hogere mortaliteit en morbiditeit ratio en heeft vaak langdurige cognitieve beperkingen, welke er voor kunnen zorgen dat de kwaliteit van leven van de patiënt vermindert. Het voorkomen van een delirium is daarom belangrijk. Haloperidol profylaxis is een antipsychotische medicatie die wordt gebruikt ter preventie van delirium. Momenteel zijn er twee gerandomiseerde gecontroleerde studies beschikbaar over de werkzaamheid van haloperidol profylaxis ter preventie van delirium voor de oudere patiënt. Deze studies laten verschillende resultaten zien. Beide studies hebben verschillende type patiënten geincludeerd wat de oorzaak kan zijn voor het verschil in uitkomsten voor de werkzaamheid van halolperidol profylaxis en de incidentie van delirium. Desondanks heeft het Centrum voor Geriatrische Traumatologie van Ziekenhuisgroep Twente vraagtekens gezet bij deze resultaten en hun beleid waarin haloperidol profylaxis werd gegeven als een preventieve behandeling voor patiënten met een verhoogd risico voor het ontwikkelen van een delirium, veranderd in een beleid waarin haloperidol profylaxis niet meer werd gegeven als een preventie behandeling.

Onderzoeksvraag
Wat is de effectiviteit van het behandelingsbeleid met of zonder haloperidol profylaxis op de incidentie van delirium, duur van ziekenhuis opname, ziekenhuis mortaliteit ratio en complicaties die optreden onder patiënten van 70 jaar of ouder met een fractuur die het Centrum voor Geriatrische Traumatologie van Ziekenhuisgroep Twente voor de eerste keer bezoeken? Eveneens wordt het effect onderzocht voor patiënten behandeld met of zonder haloperidol profylaxis.

Methode
Dit was een retrospectieve cohort studie uitgevoerd in één ziekenhuis en gericht op twee studies: een behandelingsbeleid studie en een groep studie. Geïncludeerd waren patiënten van 70 jaar of ouder met een fractuur die de spoedeisende hulp van Ziekenhuisgroep Twente voor de eerste keer hebben bezocht gedurende de studie periode (18 Maart 2008 – 7 Juni 2012) en zijn behandeld in het Centrum voor Geriatrische Traumatologie. In de behandelingsbeleid studie werd het beleid met haloperidol profylaxis (18 maart 2008 – januari 2012) vergeleken met het beleid zonder haloperidol profylaxis (februari 2012 – 7 juni 2012). In de groep studie werd de groep patiënten die behandeld zijn met haloperidol profylaxis vergeleken met de groep patiënten die niet zijn behandeld met haloperidol profylaxis. Voor beide studies zijn alle patiënten en de patiënten met een heup operatie bekeken voor de incidentie van delirium, duur van ziekenhuis opname, ziekenhuis mortaliteit ratio en de complicaties die optreden.

Resultaten
In totaal waren er 655 patiënten geincludeerd. Het beleid met haloperidol profylaxis bestaat uit 595 patiënten en het beleid zonder haloperidol profylaxis uit 60 patiënten. De incidentie van delirium van het beleid met haloperidol profylaxis was 24,0% versus 13,3% van het beleid zonder haloperidol profylaxis voor alle patiënten (RR = 1,80; 95% CI: 0,93 – 3,49). Correcties voor leeftijd en geslacht heeft dit effect niet wezenlijk veranderd. In het beleid met haloperidol profylaxis is voor alle patiënten een jaarlijkse afname te zien in de incidentie van delirium, met een incidentie van delirium in 2011 van 14,5%. De vergelijking van de incidentie van delirium van 2011 met de incidentie van 2012 resulteerde in een relatief risico van 1,09 (95% CI: 0,50 – 2,40). De incidentie

van delirium voor patiënten met een heupoperatie was 30,6% voor de patiënten van het beleid met haloperidol profylaxis en 8,6% voor de patiënten van het beleid zonder haloperidol profylaxis (RR = 3,57; 95% CI: 1,20 – 10,63). De ruwe odds ratio voor het behandelingsbeleid met haloperidol prophylaxis vergeleken met het behandelingsbeleid zonder haloperidol prophylaxis was 4,70 (95% CI: 1,41 – 15,64). Na corrigeren voor geslacht en leeftijd veranderde de odds ratio naar 5,12 (95% CI: 1,52 – 17,21). De duur van ziekenhuis opname leek voor alle patiënten en de heupoperatie patiënten langer voor het beleid met haloperidol profylaxis dan voor het beleid zonder haloperidol profylaxis, met een gemiddeld verschil van 1,5 dagen (95% CI: -1,7 – 4,6) en 2,9 dagen (95% CI: -1,2 – 6,9) respectievelijk. De ziekenhuis mortaliteit ratio was 5,4% versus 0,0% voor alle patiënten en 9,8% versus 0,0% voor heupoperatie patiënten. De incidentie van complicaties die optreden was 48,2% voor het beleid met haloperidol profylaxis versus 46,7% voor het beleid zonder haloperidol profylaxis voor alle patiënten (RR = 1,03; 95% CI: 0,78 – 1,37) en 57,4% versus 48,6% voor heupoperatie patiënten (RR = 1,18; 95% CI: 0,83 – 1,68).

De groep met haloperidol profylaxis bestaat uit 216 patiënten en de groep zonder haloperidol profylaxis bestaat uit 439 patiënten. De incidentie van delirium van de groep met haloperidol profylaxis was 51,9% versus 8,9% in de groep zonder haloperidol profylaxis voor alle patiënten (RR = 5,84; 95% CI: 4,21 – 8,09). De ruwe odds ratio was 11,05 (95% CI: 7,23 – 16,87). Na correcties voor leeftijd en geslacht, de odds ratio veranderde naar 9,36 (95% CI: 6,08 – 14,40). Voor heupoperatie patiënten was de incidentie van delirium 52,8% voor de groep met haloperidol profylaxis versus 12,1% voor de groep zonder haloperidol profylaxis (RR = 4,38; 95% CI: 3,05 – 6,24). De ruwe odds ratio was 8,12 (95% CI: 5,04 – 13,09) en na correcties voor leeftijd en geslacht veranderde de odds ratio naar 7,06 (95% CI: 4,34 – 11,48). Het gemiddelde verschil in duur van ziekenhuis opname was 2,0 dagen (95% CI: 0,1 – 4,0) voor de groep met haloperidol profylaxis in vergelijking met de groep zonder haloperidol profylaxis voor alle patiënten. Voor heupoperatie patiënten het gemiddelde verschil was 1,8 dagen (95% CI: -0,4 – 4,1). De ziekenhuis mortaliteit ratio was voor alle patiënten 7,9% versus 3,4% (RR = 2,30; 95% CI: 1,17 – 4,52) en voor heupoperatie patiënten 7,9% versus 4,7% (RR = 1,68; 95% CI: 0,80 – 3,54). Het aantal complicaties wat optreedt was voor alle patiënten 58,8% in de groep met haloperidol profylaxis versus 42,8% in de groep zonder haloperidol profylaxis (RR = 1,37; 95%CI: 1,18 – 1,60) en voor heupoperatie patiënten 62,9% versus 52,3% (RR = 1,20; 95% CI: 1,02 – 1,40).

Conclusie

De incidentie van delirium lijkt hoger te zijn voor het behandelingsbeleid met haloperidol profylaxis in vergelijking met het behandelingsbeleid zonder haloperidol profylaxis voor alle patiënten en vooral voor heupoperatie patiënten. De duur van ziekenhuis opname leek langer en de ziekenhuis mortaliteit ratio leek hoger voor het beleid met haloperidol profylaxis. De complicaties die optraden waren hoger voor heupoperatie patiënten in het beleid met haloperidol profylaxis in vergelijking met het beleid zonder haloperidol profylaxis.

De incidentie van delirium in de groep met haloperidol profylaxis vergeleken met de groep zonder haloperidol profylaxis liet een duidelijk verschil zien voor alle patiënten en heupoperatie patiënten. Een patiënt in de groep met haloperidol profylaxis had een hoger risico om een delirium te ontwikkelen dan een patiënt in de groep zonder haloperidol profylaxis. De duur van ziekenhuis opname was langer en de ziekenhuis mortaliteit ratio was hoger voor alle patiënten in de groep met haloperidol profylaxis. De incidentie van complicaties die optreden was hoger voor alle patiënten en heupoperatie patiënten in de groep met haloperidol profylaxis vergeleken met de patiënten in de groep zonder haloperidol profylaxis.

De effectiviteit van haloperidol profylaxe ter preventie van delirium blijft onduidelijk. De belangrijkste beperking van deze studie en de bijhorende resultaten is het feit dat alleen correcties konden worden gemaakt voor de risico factoren leeftijd en geslacht. De andere risico factoren waren niet geregistreerd, waardoor er niet voor kon worden gecorrigeerd. De resultaten van deze studie moeten daarom voorzichtig worden geïnterpreteerd. Verder onderzoek naar de effectiviteit van haloperidol profylaxis op de incidentie van delirium is noodzakelijk.

Trefwoorden: *haloperidol profylaxis, preventie, delirium, ouderen, geriatrisch fractuur centrum*

Content

Introduction

Delirium is a common mental disorder which can lead to problems with consciousness, attention, memory, thought, behavior and a disturbance in orientation.[1-3] In the Netherlands the prevalence of delirium lies between 100,000 and 150,000 patients per year.[3] Delirium manifests acutely, lasts hours to days, and tends to fluctuate over time showing generally worse symptoms during the night.[4,5] A healthcare professional can miss to recognize a delirium. A Canadian research of 1996 shows that 48% of patients known with a delirium are recognized on a psychiatric ward.[3] English research of 1997 shows that in a common hospital 46% patients with a delirium are not recognized by the general physicians.[3] The symptoms can be easily missed due to the fluctuation of symptoms.[6] In diagnosing the elderly patient the delirium can be confused with dementia or a depression.[3,6]

Causes for a delirium can be a combination of a patients vulnerability at hospital admission and provoking factors that the patient endures during hospitalization. A patients vulnerability is characterized by underlying medical conditions (e.g. an infection), substance use or withdrawal or unknown causes.[5] Provoking factors during hospitalization include an operation, hospitalization at the Intensive Care (IC), insomnia and prescribed medication (especially medication like benzodiazepines and opioids).[4,7,8] The risk factors for a delirium include age (above 65 years), dementia, co-morbidity, visual or hearing impairment, alcohol abuse, medication use and depression.[4,9]

The implications of delirium can lead to a greater morbidity, greater mortality, longer nursing time per patient, higher hospital costs per day, longer length of hospital stay and persistent functional decline compared to the patient without a delirium. The risk of mortality rises with 62% when a patient develops a delirium.[10] The incidence of delirium developed after surgery is 36,8% for all patients and is particularly high for patients at risk.[11,12]

Delirium is a serious problem for the elderly hospitalized patients.[13] The prevalence of delirium increases with age.[11] The incidence for the elderly postoperative patient ranged from 15% to 53% and for patients in need of intensive care the incidence was between 50% and 80%.[11,14] The patient with a delirium suffers worse health outcomes as mentioned above e.g. longer hospital stay, higher mortality and morbidity rate than the patient without a delirium. The occurrence of delirium has also negative impacts on the long term. The patient tends to have a long-term cognitive impairment and it is likely that the quality of life reduces.[11] Taken all these negative impacts of delirium into account, it is important to prevent delirium. Prevention of delirium can be divided in three categories: medication review, non pharmacological interventions and pharmacological measures.[2] One of the pharmacological interventions provided to prevent delirium is haloperidol.[15]

Haloperidol is an antipsychotic drug and is used for the treatment of delirium.[15,16] Caution with antipsychotic drugs is necessary, because they can make the delirium worse and underlying causes can exacerbate. Haloperidol is less likely to worsen delirium, because it is a high potency drug which is less sedative than some other antipsychotic drugs, such as phenothiazines. However, it is prone to cause parkinsonism, which can increase the tendency to fall for a patient.[5] The side effects e.g. hypotension, sedation, extra pyramidal symptoms, altered cardiac conduction and others of haloperidol depends on dosage. Therefore it is wise to keep the dose as low as possible.[11,16] It is unknown what the optimal dosage of haloperidol is.[3,17]

Currently there are two randomized controlled trials (RCTs) available that examine the efficacy of haloperidol on the prevention of delirium for elderly patients. The first RCT (2005) is performed in a large medical school affiliated general hospital in the Netherlands. 430 Patients of 70 years and older with a hip fracture participated. This study shows that haloperidol is not effective in preventing delirium for the haloperidol group versus the placebo group (RR = 0,91, 95% CI: 0,6-1,3). It however reduces the severity and duration of delirium

and decreases the length of hospital stay.[1,6,15] In this study haloperidol was given 3 times a day (0.5 mg), started preoperatively and lasted till 3 days after surgery and was conducted with hip surgery patients. The overall incidence of postoperative delirium was 15,8%.[11] The second RCT (2012) is performed in intensive care units of two large tertiary teaching hospitals in China. 457 Patients aged 65 years and older who were admitted to the intensive care unit after noncardiac surgery participated in this study. The patients were administered a low dose intravenous haloperidol (0,5 mg) for 7 days. The incidence of delirium decreased significantly (p=0,031). The incidence in the haloperidol group was 15,3% versus 23,2% in the control group.[13] The mean time to onset of delirium and the number of delirium-free days were significantly longer for the haloperidol group, whereas the length of stay at the IC was significantly shorter for the haloperidol group.

The literature findings described above show conflicting results about the efficacy of haloperidol; one study states that the incidence of delirium is decreased and the other study shows that the incidence does not decrease. This can be caused by the different type of patients included; patients with a hip fracture versus intensive care patients. These conflicting results about the efficacy of haloperidol on the prevention of delirium, the Center for Geriatric Traumatology (CGT) of the Ziekenhuisgroep Twente (ZGT) situated in Almelo, the Netherlands, caused a change in their policy regarding the prevention of delirium. The CGT (founded in 2008) is a multidisciplinary treatment concept that provides intensive care for elderly patients during their entire treatment; from entering the emergency department until their clinical follow-up. This treatment consists of a multidisciplinary approach and clinical pathways with a special focus on geriatric related aspects such as delirium.[18] Since March 2008 the CGT gave haloperidol prophylaxis to patients at risk for developing a delirium. After the conflicting results in the literature regarding the efficacy of haloperidol, the CGT stopped in February 2012 with providing haloperidol prophylaxis to their elderly patients at risk for developing a delirium.

Research question

The CGT changed their policy to give haloperidol prophylaxis to prevent delirium to a policy where haloperidol prophylaxis is not given as a prevention for delirium, due to the conflicting results about the effect of haloperidol prophylaxis in preventing delirium in the literature. The CGT wants the best care for their patients and sees the importance to study this matter to make sure that changing their policy is the right decision and hopes to provide a contribution to the current knowledge about the efficacy of haloperidol prophylaxis on the incidence of delirium in the literature. This leads to the following research question:

What is the efficacy of the treatment policy with or without haloperidol prophylaxis on the incidence of delirium, length of hospital stay, hospital mortality rate and complications that occur among patients aged 70 years and older with a fracture that visit the Center for Geriatric Traumatology (CGT) of Ziekenhuisgroep Twente (ZGT) for the first time? Similarly, the effect is assessed for patients treated with or without haloperidol prophylaxis.

Methods

Study design & patients

This was a single center retrospective study that focused on two cohort studies. In the first study the included patients were divided in two treatment policies (treatment policy with or without haloperidol) and in the second study the patients were divided in two groups (group with or without haloperidol). Included for both studies were patients aged 70 years and older who entered the emergency ward at the ZGT, location Almelo, for the first time during the study period (March 2008 till June 7th 2012) with a fracture and were treated at the CGT by the multidisciplinary team.

In the first study two treatment policies were compared. Patients of the first treatment policy at risk for developing a delirium were given haloperidol prophylaxis, 3 times a day 0,5 mg haloperidol prophylaxis during 3 days, to prevent the development of a delirium. A patient was considered at risk for developing a delirium when the patient scored 3 out of 10 predisposing factors of the Delirium Observation Scale (DOS). The predisposing factors of DOS are: history of a delirium, cognitive malfunctioning, change in opioid analgesics, more than 4 units of alcohol a day, age above 70 years, use of drugs, fever of 38,5°C or higher, metabolic disorder, deafness and visual impairment and whether the surgery is under narcosis.[19] This treatment policy with haloperidol prophylaxis was implemented in March of 2008 and carried out till February 2012. Since February 2012 till June 7th 2012 a different treatment policy was implemented: the patients were not provided with haloperidol prophylaxis even when they were at risk for developing a delirium. The only difference between the two treatment policies was the use of haloperidol prophylaxis, furthermore the two policies remained identical.

The study aim was to evaluate the efficacy of a treatment policy with haloperidol prophylaxis versus a treatment policy without haloperidol prophylaxis on the prevention of delirium in geriatric care. The two treatment policies were also compared with regard to other outcome measures: length of hospital stay, hospital mortality rate and complications that occur during treatment. After these analyses on all patients included in this study, the inclusion criteria were limited to surgery patients and later to hip surgery patients. The surgery patients were studied on the incidence of delirium, with a special focus on the hip surgery patients for the incidence of delirium and the other outcomes. See figure 1 for the study design for both studies.

In the second study, all included patients during the entire period were split in two groups: a group of patients that received haloperidol prophylaxis and a group of patients that did not receive haloperidol prophylaxis. In this study the same analyses as in study 1 were performed.

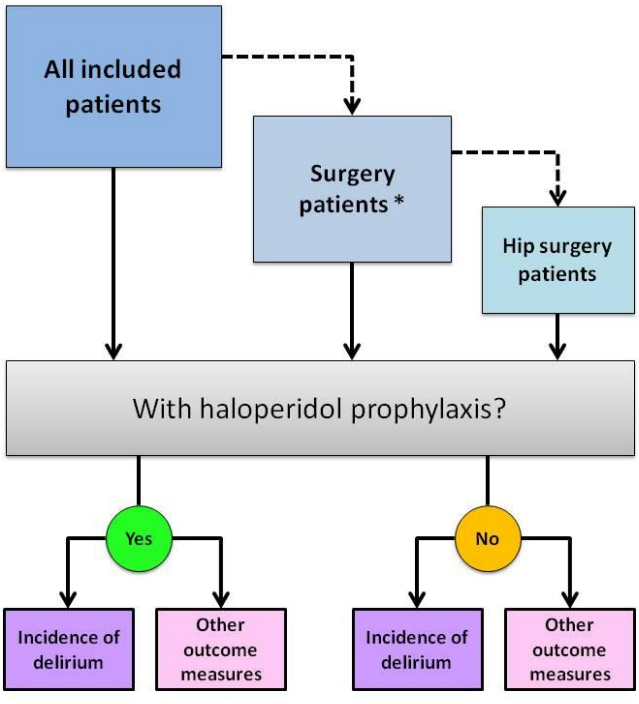

Figure 1. Study design for both studies

Outcome assessments

The data for this study has been collected since the start of the CGT in 2008 by healthcare professionals of the CGT and their secretary assistance. In a database called Thinkwise, data of all CGT patients is collected. Thinkwise consists of four different databases; fractures, complications, analysis and advice. Each database consists of common information about the patient; age, gender, patient identification number, date of birth and admission and discharge date. In the database fractures different fracture and treatment types are registered, as well as information regarding delirium and haloperidol prophylaxis. The database complications recorded the complications that occurred during hospitalization. The database analysis recorded information concerning the multidisciplinary treatment and provided some information on the medical background of the patient, for example whether the patient suffered dementia. Finally, the database advice recorded information regarding delirium, haloperidol prophylaxis, medication use, dementia and some lab functions. Only the data of the databases fractures and complications was used for this study, since these databases give information about patients during the whole study period, except for the months May and June of 2011. These two months were missing in the data due to a transition of the Rochester database to Thinkwise in this period. The data of the other two databases (analysis and advice) in Thinkwise were incomplete; the last data is from 2009. In SPSS the two useable databases of Thinkwise were merged into one SPSS database.

The primary outcome of this research was the cumulative incidence of delirium. Information about delirium was listed in the fracture database as well as the complications database in Thinkwise and were listed differently in the merged SPSS database. The information about delirium from the fracture database was listed as a number and from the complications database as text. This text was converted to a number, where 1 represented a delirium and 0 represented that no delirium manifested. This way the information about delirium from fractures and complications could be combined in “delirium total”. Diagnosis of delirium was confirmed when the “delirium total” scores 1 or 2 and a zero means that no delirium was present during hospitalization. In “delirium total” there was missing data. Of 95 patients no data was available. For these missing values it was assumed that a delirium did not manifest. The information about the use of haloperidol prophylaxis consisted also of missing values; for 148 patients no data was present. For these missing values it was also assumed the patient did not get haloperidol prophylaxis.

Secondary outcome measures included length of hospital stay, hospital mortality rate and complications that occur among patients during hospitalization. Length of hospital stay is the actual time the patient stayed in the hospital. This was calculated by subtracting the admission date (day of admission at the emergency department) from the discharge date. For 18 patients there was an error in the dates which resulted in negative or extreme values in the length of hospital stay; these values were set as missing values. The hospital mortality rate is registered after the patient was submitted to the emergency ward and was retrieved from the complications database where it was listed as text. This text is converted to a number where 0 represents that the patient did not die and 1 represents that the patient deceased. The cumulative incidence of complications was retrieved from the complications database. In this database the complications were divided in different types of complications, such as heart failure, pneumonia and urinary tract infection. These complications or combinations of complications were converted from text to the number 1, so the incidence of one or more complications that occurred during hospitalization could be calculated.

The mentioned outcomes were for the treatment policy study (treatment policy with and without haloperidol prophylaxis) and the group study (group with and without haloperidol prophylaxis) for all included patients, with a focus on hip surgery patients. See figure 1 for an overview. For the treatment policy study, the assumption was made that the treatment policy with haloperidol prophylaxis and the treatment policy without haloperidol prophylaxis were similar treatment policies, except for the haloperidol prophylaxis usage. Furthermore, both treatment policies were composed of the same type of patients and could therefore be

compared. For the group study, the two groups, group with haloperidol prophylaxis and group without haloperidol prophylaxis, did not consist of the same type of patients. The group with haloperidol prophylaxis most likely consisted of patients that were at risk for developing a delirium and may had worse health symptoms. The distribution of patients between the haloperidol prophylaxis group and the group without haloperidol prophylaxis might have been different, which would cause a limited comparison.

Statistical analysis

Continuous variables with a normal distribution were compared between groups by using the independent samples t-test, otherwise with the Mann-Whitney U test. Categorical variables were compared between groups by using the Chi-square analysis or Fisher exact test. The Fisher exact test is used if the expected values of a cell is smaller than 5. Two tailed p-values <.05 indicated statistical significance. The results are given with the p-value and the relative risks (RR) with 95% confidence intervals (CIs) or a mean difference with 95% confidence interval. The relative risks were based on cumulative outcome measures. For instance, the cumulative incidence of delirium is the amount of patients in a group that have developed a delirium, divided by the total amount of patients included in the same group. In the treatment policy study the RR or the mean difference was for the treatment policy with haloperidol prophylaxis relative to the treatment policy without haloperidol prophylaxis. For the group study, the RR or the mean difference was for the group with haloperidol prophylaxis relative to the group without haloperidol prophylaxis. There was no significant difference when 1 lies in the confidence interval of the relative risk. For the mean difference there was no significant difference when 0 lies in the confidence interval.
A binary logistic regression model was used to determine whether the association between the treatment policy study or the group study and the primary outcome was confounded by baseline differences and known risk factors. These variables were entered into the logistic model. Statistical analyses were performed using SPSS for Windows, version 20 (SPSS, Inc., Chicago, IL).

Results

TREATMENT POLICY STUDY. Treatment policy with haloperidol prophylaxis compared to the treatment policy without haloperidol prophylaxis

Patient characteristics

A total of 655 patients were included in this study to compare the treatment policy with haloperidol prophylaxis to the treatment policy without haloperidol prophylaxis. Excluded from this research were patients who did not meet the inclusion criteria, for whom important data (age, gender and birth- and admission date) was missing and patients with errors in the data (incorrect dates and duplicate data). See figure 2.

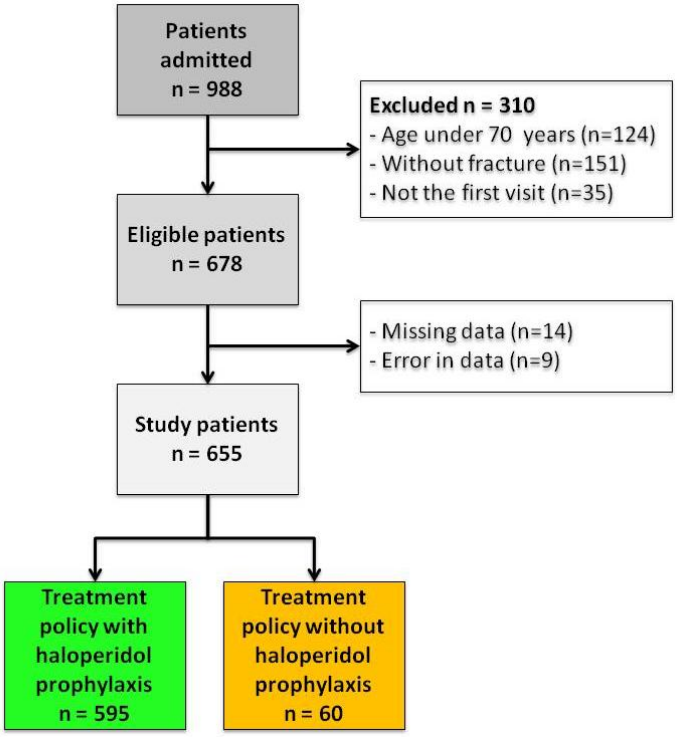

Figure 2. Flow diagram of the study

Baseline characteristics of patients receiving care according to both treatment policies, the treatment policy with haloperidol prophylaxis and the treatment policy without haloperidol prophylaxis, are shown in table 1. The treatment policy with haloperidol prophylaxis consisted of 595 patients and the treatment policy without haloperidol prophylaxis consisted of 60 patients. The treatment policy with haloperidol prophylaxis was implemented from March 18th 2008 till February 2012 and the treatment policy without haloperidol prophylaxis from February 2012 till June 7th 2012. The baseline characteristics of both groups were almost similar. However, there was a difference regarding the type of fracture. There were more hip fractures in the treatment policy with haloperidol prophylaxis (79,2%) than in the treatment policy without haloperidol prophylaxis (63,3%) ($p = 0,017$). Consequently, there were relatively less upper extremity fractures (8,4%) in the group with the haloperidol prophylaxis policy compared to the group without haloperidol prophylaxis policy (23,9%).

Table 1. Characteristics of all patients			
Characteristic	*Treatment policy with haloperidol prophylaxis (n = 595)*	*Treatment policy without haloperidol prophylaxis (n = 60)*	*P - value*
Gender, n (%)			0,65 [1]
• Women	440 (73,9)	46 (76,7)	
• Men	155 (26,1)	14 (23,3)	
Age, mean (SD)	82,04 (6,49)	81,13 (6,65)	0,30 [2]
Submitted from, n (%)			0,24 [3]
• Home	199 (36,1)	24 (40,0)	
• Home with care	193 (35,0)	26 (43,3)	
• Nursing home	80 (14,5)	4 (6,7)	
• Home for the elderly	72 (13,1)	5 (8,3)	
• Other	7 (1,3)	1 (1,7)	
Length of stay at emergency ward in minutes, mean (SD)	134,39 (164,29)	145,56 (134,5)	0,63 [2]
Time till operation in hours, mean (SD)	30,28 (57,56)	39,52 (75,29)	0,46 [4]
Fracture group, n (%)[#]			**<0,05** [3]
• Hip / pelvis	471 (79,2)	38 (63,3)	
• Upper extremity	50 (8,4)	14 (23,9)	
• Lower extremity	44 (7,4)	3 (5,0)	
• Upper extremity / hips / pelvis	9 (1,5)	3 (5,0)	
• Other (combinations of) fractures	21 (3,5)	2 (2,8)	
Fracture type hip and pelvis, n (%)[#^]			0,38 [3]
• Medial collum	243 (49,5)	19 (45,2)	
• Petr. Femur	192 (39,1)	15 (35,7)	
• Subt. Femur	15 (3,1)	2 (4,8)	
• OS pubis ramus inf./OS pubis ramus sup.	17 (3,5)	3 (7,1)	
• Other	24 (4,8)	3 (7,2)	
Treatment type hip and pelvis, n (%)[^]			0,72 [3]
• IM Pen hip	167 (39,7)	17 (44,7)	
• Hemi arthro plastic hip	139 (33,0)	10 (26,3)	
• Plate osteo synthesis hip	78 (18,5)	8 (21,1)	
• Other	37 (8,8)	3 (7,9))	
Fracture type lower extremity, n (%)[#^]			0,10 [3]
• Ankle	23 (43,4)	1 (25)	
• Foot	6 (11,3)	1 (25)	
• Other	24 (45,4)	2 (50)	
Treatment type lower extremity, n (%)[^]			**<0,05** [3]
• IM pen femur	77 (63,1)	0 (0)	
• Plate / screw osteo synthesis ankle	16 (13,1)	1 (25,0)	
• Cast	7 (5,7)	2 (50,0)	
• Other	22 (18,1)	1 (25,0)	
Fracture type upper extremity, n (%)[#^]			0,30 [3]
• Distal radius / ulna	14 (35,0)	5 (38,5)	
• Proximal humerus	20 (50,0)	4 (30,8)	
• Other	6 (15,0)	4 (30,7)	
Treatment type upper extremity, n (%)[^]			0,75 [3]
• Plate wrist	6 (10,3)	4 (25,0)	
• Plate proximal humerus	8 (13,8)	2 (12,5)	
• Sling	7 (12,1)	3 (18,8)	
• Sling / other	6 (10,3)	2 (12,5)	
• Other	31 (53,5)	5 (31,2)	

The N of fracture types, hip, lower- and upper extremity, does not correspond with the N of the fracture group due to the combinations of fractures in the fracture group.

^ The N of the fracture type does not correspond with the N of the treatment type of the same fracture type, due to missing values in the data.

[1] Chi square test

[2] Independent t-test

[3] Fisher exact test

[4] Mann-Whitney U test

Efficacy of the treatment policies on the incidence of delirium

The incidence of delirium in the treatment policy with haloperidol prophylaxis was 24,0% versus 13,3% in the treatment policy without haloperidol prophylaxis (table 2). The group with the haloperidol prophylaxis policy had a higher risk of developing a delirium than the group without the haloperidol prophylaxis policy. The relative risk was 1,80 with a 95% CI of 0,93 – 3,49. For the treatment policy with haloperidol prophylaxis the incidence per year was studied. After the implementation of the treatment policy with haloperidol prophylaxis each year a decrease in the incidence of delirium could be seen. Comparing the incidence of delirium of the year 2011 of the treatment policy with haloperidol prophylaxis to the treatment policy without haloperidol prophylaxis the incidence was 14,5% versus 13,3% respectively, with a relative risk of 1,09 (95% CI: 0,50 – 2,40).

Table 2. Efficacy of the treatment policy with haloperidol prophylaxis versus the treatment policy without haloperidol prophylaxis

	Treatment policy with haloperidol prophylaxis (n = 595)	*Treatment policy without haloperidol prophylaxis (n = 60)*	*P - value*	*RR (95% CI) or mean difference (95% CI)*
Incidence of delirium, n (%)	143 (24,0)	8 (13,3)	0,06 [1]	1,80 (0,93 - 3,49)
• *Year 2008 (n = 115)*	*37 (32,2)*			
• *Year 2009 (n = 141)*	*42 (29,8)*			
• *Year 2010 (n = 219)*	*43 (19,6)*			
• *Year 2011 (n = 110)*	*16 (14,5)*			
Length of hospital stay in days, mean (SD)+	13,2 (12,2)	11,7 (7,4)	0,36 [2]	1,5 (-1,7 – 4,6)
• *Year 2008 (n = 112)*	*13,5 (12,1)*			
• *Year 2009 (n = 138)*	*13,6 (9,2)*			
• *Year 2010 (n = 214)*	*11,7 (11,9)*			
• *Year 2011 (n = 103)*	*15,2 (15,9)*			
Hospital mortality rate, n (%)	32 (5,4)	0 (0,0)	0,11 [3]	-
Complications, n (%)*	287 (48,2)	28 (46,7)	0,82 [1]	1,03 (0,78 – 1,37)

+ N = 638, with n = 578 for the treatment policy with haloperidol prophylaxis and n = 60 for the treatment policy without haloperidol prophylaxis

* One or more complications

[1] Chi square test - [2] Independent t-test - [3] Fisher exact test

Distribution of incidence of delirium per month

The incidence of delirium of a large group of patients, covering almost four years, was compared to a small group of patients which covered just over four months (February till June 7th). To be certain the months February till June 7th could be compared to all months of four years, an analysis was performed to compare the incidence of delirium per month (figure 3). The treatment policy with haloperidol prophylaxis was used for this analysis and showed a small fluctuation over the months. The chi square test showed a p-value of 0,91. There was no difference for the incidence of delirium per month over the years. This means that it was justified to compare both treatment policies with the different corresponding study periods. For each year separately a fluctuation over the months was also found with no difference between the months on the incidence of delirium.

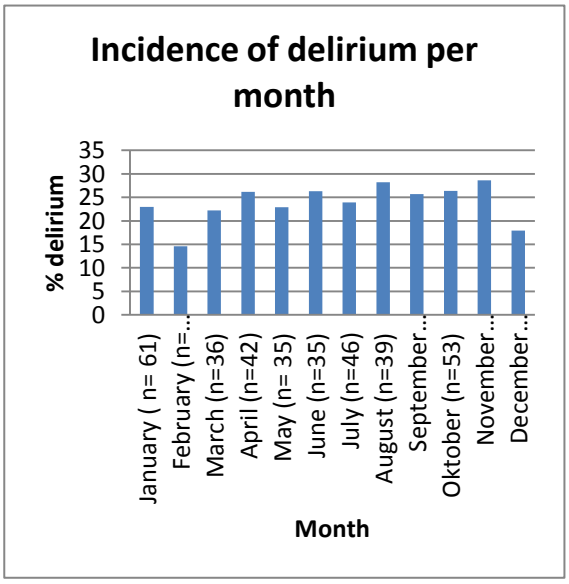

Figure 3. Incidence of delirium per month

Influencing factors on the incidence of delirium

As stated in table 2 the treatment policy with haloperidol prophylaxis had a higher risk (RR = 1,80 with a 95% CI of 0,93 – 3,49) for developing a delirium than the treatment policy without haloperidol prophylaxis. Possible confounders on this relative risk between the treatment policy with haloperidol prophylaxis and the treatment policy without haloperidol prophylaxis on the incidence of delirium could have been age and gender.

The incidence of delirium increased with age (figure 4). Patients in the age of 80 were more at risk for developing a delirium than patients in their early seventies. The Fisher's exact test showed a significant difference between age and the incidence of delirium ($p < 0,001$).

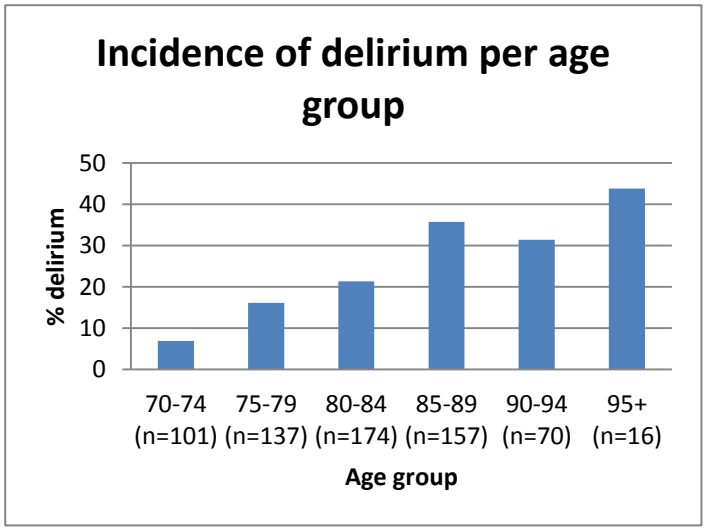

Figure 4. Incidence of delirium per age group

The relationship between age and the treatment policy with haloperidol prophylaxis and the treatment policy without haloperidol prophylaxis should be studied as well. According to the independent T- test there is no relationship between age and both treatment policies; $p = 0,30$ (difference = 0,9; 95% CI: -0,8 – 2,6). Age is likely not a confounder in this study between the treatment policy with haloperidol prophylaxis and without haloperidol prophylaxis and the incidence of delirium.

Another potential confounder could have been gender. In table 1 it was shown that there is no difference between gender and the treatment policy with or without haloperidol prophylaxis (p= 0,65; RR = 0,99; 95% CI: 0,94 – 1,04). The relationship between gender and the incidence of delirium resulted in no significant difference with the Chi square test ($p = 0,20$). Of the included woman 21,8% developed a delirium and 26,6% of the men developed a delirium during hospitalization. The relative risk for a woman to develop a delirium compared to a man was 0,82 (95% CI: 0,61 – 1,11). Gender is also likely not a confounder between the treatment policy with and without haloperidol prophylaxis and the incidence of delirium.

Both age and gender were not considered to be a confounder for the incidence of delirium. Nonetheless, both were entered in a logistic regression model to see the influence on the odds ratio (OR). The crude OR for the treatment policy with and with haloperidol prophylaxis on the incidence of delirium was 2,06 (95% CI: 0,95 – 4,43). Adjusted for gender the OR changed to 2,04 (95% CI: 0,95 – 4,40). Adjusted for age the OR was 1,98 (95% CI: 0,90 – 4,34). Adjusted for both age and gender the OR changed to 1,98 (95% CI: 0,90 – 4,34). Adjusting for age and gender had an influence on the OR for the incidence of delirium, although not significantly.

Efficacy of the treatment policies on the other outcome measures

The length of hospital stay was available for 638 patients and showed a small difference between the two treatment policies. The treatment policy with haloperidol prophylaxis resulted in a longer hospital stay than the treatment policy without haloperidol prophylaxis. The mean differs with more than a day for the length of hospital stay (difference = 1,5 days; 95% CI of -1,7 – 4,6). For the treatment policy with haloperidol prophylaxis the length of hospital stay was also studied for four years separately. No trend was found; 2010 (mean of 11,7 days) showed a decrease in comparison to 2009 (mean of 13,6 days), however in 2011 (mean of 15,2 days) the length of hospital stay increased again.
The hospital mortality rate showed no significant difference, with 9,6% deceased patients in the group with the haloperidol prophylaxis policy and 0,0% deceased patients in the treatment policy without haloperidol prophylaxis. Caution is necessary interpreting this result, because of the small number of patients.
The amount of patients that endured one or more complications showed no significant difference between both groups, 48,2% for the treatment policy with haloperidol prophylaxis and 46,7% for the treatment policy without haloperidol prophylaxis. The patients of the haloperidol prophylaxis policy had a similar risk of developing a complication as the patients of the treatment policy without haloperidol prophylaxis (RR = 1,03; 95% CI: 0,78 – 1,37).

Patients with surgery

The analyses were further limited to patients that had a surgery during their hospitalization. Of the 655 patients used in the policy study, 530 patients had surgery during hospitalization. Of these surgery patients 25,3% developed a delirium.
Of the 530 surgery patients 485 patients were in the policy with haloperidol and 45 patients were in the policy without haloperidol. The incidence of delirium for surgery patients of the policy with haloperidol was 27,0% and for the policy without haloperidol 6,7%. This was a significant difference ($p < 0,01$). With a relative risk of 4,05 (95% CI: 1,35 – 12,21) patients of the policy with haloperidol had a higher risk to develop a delirium than the patients of the policy without haloperidol.

The crude OR for the treatment policy with and without haloperidol prophylaxis on the incidence of delirium was 5,18 (95% CI: 1,58 – 17,00). Adjusted for gender the OR changed to 5,18 (95% CI: 5,18 – 16,99). Adjusted for age the OR was 5,03 (95% CI: 1,50 – 16,88). Adjusted for both age and gender the OR changed to 5,12 (95% CI: 1,52 – 17,21). Adjusting for age and gender had an influence on the OR for the incidence of delirium for surgery patients.

Patients with a hip surgery

The analyses were further limited to patients with a hip surgery. Of the 530 surgery patients, 434 patients had a hip surgery (81,9%). Of the hip surgery patients 28,8% developed a delirium.
The policy with haloperidol consisted of 399 patients and the policy without haloperidol of 35 patients (table 3). The incidence of delirium was 30,6% for the policy with haloperidol versus 8,6% for the group without haloperidol. The risk of developing a delirium was higher in the policy with haloperidol group with a relative risk of 3,57 (95% CI: 1,20 – 10,63); a significant difference.
The incidence of delirium shows a fluctuation over the years separately, with the lowest incidence of delirium in 2011 (22,5%). Comparing the treatment policy with haloperidol prophylaxis of year 2011 with the treatment policy without haloperidol prophylaxis (2012), resulted in a RR of 2,62 (95% CI: 0,77 – 8,94).

The crude OR for the treatment policy with and without haloperidol prophylaxis on the incidence of delirium was 4,70 (95% CI: 1,41 – 15,64). Adjusted for gender the OR changed to 4,70 (95% CI: 1,41 – 15,65). Adjusted for age the OR changed to 5,15 (95% CI: 1,51 – 17,54). After adjusting for both gender age, the OR changed to 5,26 (95% CI: 1,54 – 17,98). The risk factors gender and age had an influence on the OR for the incidence of delirium for hip surgery patients.

Table 3. Efficacy of the treatment policy with haloperidol prophylaxis versus the treatment policy without haloperidol prophylaxis for hip surgery patients

	Treatment policy with haloperidol prophylaxis (n = 399)	*Treatment policy without haloperidol prophylaxis (n = 35)*	*P - value*	*RR (95% CI) or mean difference (95% CI)*
Incidence of delirium, n (%)	122 (30,6)	3 (8,6)	**< 0,01** [1]	3,57 (1,20 – 10,63)
• *Year 2008 (n = 107)*	*35 (32,7)*			
• *Year 2009 (n = 130)*	*37 (28,5)*			
• *Year 2010 (n = 113)*	*36 (31,9)*			
• *Year 2011 (n = 40)*	*9 (22,5)*			
Length of hospital stay in days, mean (SD)[+]	13,8 (12,0)	10,9 (5,2)	0,16 [2]	2,9 (-1,2 – 6,9)
• *Year 2008 (n = 105)*	*13,5 (12,4)*			
• *Year 2009 (n = 129)*	*13,9 (9,1)*			
• *Year 2010 (n = 111)*	*11,6 (8,2)*			
• *Year 2011 (n = 39)*	*20,9 (22,5)*			
Hospital mortality rate, n (%)	26 (9,8)	0 (0,0)	0,38 [3]	-
Complications, n (%)*	229 (57,4)	17 (48,6)	0,31 [1]	1,18 (0,83 – 1,68)

+ N = 428, with n = 393 for the policy with haloperidol and n = 35 for the policy without haloperidol
* One or more complications
[1] Chi square test
[2] Independent t-test
[3] Fisher exact test

The length of hospital stay was longer for the treatment policy with haloperidol prophylaxis than for the treatment policy without haloperidol prophylaxis; respectively 13,8 days versus 10,9 days. The different years of the treatment policy with haloperidol prophylaxis separately did not show a trend in the length of hospital stay. In the year 2010 (mean of 11,6 days) a decrease in the length of hospital stay was noticed, only to be increased in the year 2011 (mean of 20,9 days).

The hospital mortality rate showed no significant difference. For this outcome caution in interpreting the results is necessary due to the small number of patients. In the treatment policy with haloperidol prophylaxis 9,8% of the patients deceased and 0,0% of the patients deceased in the treatment policy without haloperidol prophylaxis.

The incidence of complications that occurred during hospitalization was 57,4% for the treatment policy with haloperidol prophylaxis and 48,6% for the treatment policy without haloperidol prophylaxis. The relative risk was 1,18 with a 95% CI that lies between 0,83 – 1,68. A patient of the treatment policy with haloperidol prophylaxis had a higher risk to develop a complication during hospitalization than a patient of the treatment policy without haloperidol prophylaxis, although not significantly.

PATIENT GROUP STUDY. Patients treated with haloperidol prophylaxis compared to patients treated without haloperidol prophylaxis

Patient characteristics

In this analysis all 655 patients were divided over two groups; group of patients that did get haloperidol prophylaxis and a group that did not get haloperidol prophylaxis during hospitalization. The group with haloperidol prophylaxis consisted of 216 patients and the group without haloperidol prophylaxis consisted of 439 patients (see figure 5). The study period was from March 2008 till June 7th of 2012. Baseline characteristics of these two groups are shown in table 4. More than half of the baseline characteristics showed a significant difference between the group with haloperidol prophylaxis and the group without haloperidol prophylaxis. These differences included age, the home situation of the patient, the length of stay at the emergency ward, the time till operation, the fracture group, fracture type of a hip fracture and the treatment type of the lower extremity. Despite these differences, both groups were studied on the incidence of delirium and the other outcome measures.

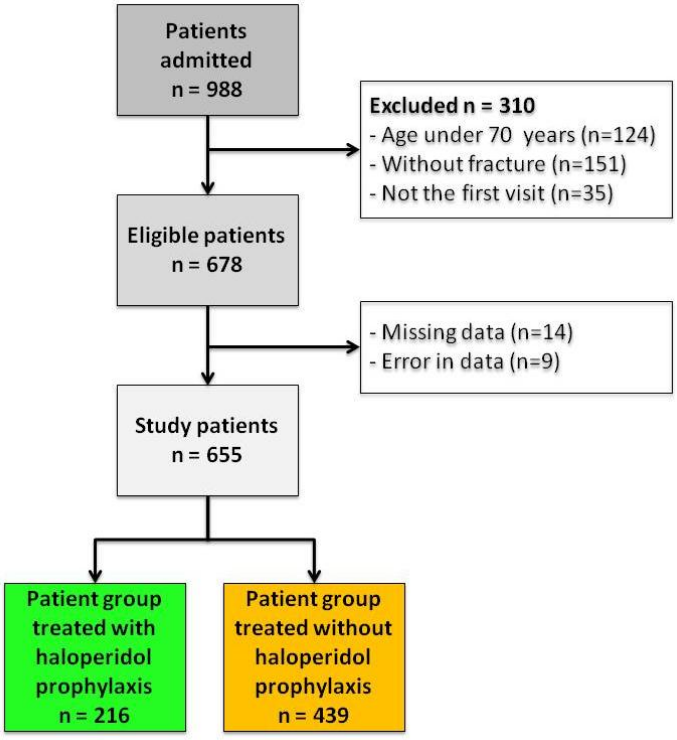

Figure 5. Flow diagram of study

Table 4. Characteristics of all patients			
Characteristic	*Group with haloperidol prophylaxis (n = 216)*	*Group without haloperidol prophylaxis (n = 439)*	*P - value*
Gender, n (%)			0,17 [1]
• Women	153 (70,8)	333 (75,9)	
• Men	63 (29,2)	106 (24,1)	
Age, mean (SD)	84,28 (5,97)	80,82 (6,45)	**<0,001** [2]
Submitted from, n (%)			**<0,001** [3]
• Home	31 (15,3)	192 (46,9)	
• Home with care	71 (35,1)	148 (36,2)	
• Nursing home	60 (29,7)	24 (5,9)	
• Home for the elderly	36 (17,8)	41 (10,0)	
• Other	4 (2,1)	4 (1,0)	
Length of stay at emergency ward in minutes, mean (SD)[+]	117,11 (120,64)	145,15 (179,34)	**< 0,05** [2]
Time till operation in hours, mean (SD)[~]	21,25 (37,54)	36,74 (68,08)	**0,01** [2]
Fracture group, n (%)[#]			**<0,001** [3]
• Hip / pelvis	195 (90,3)	314 (71,5)	
• Upper extremity	9 (4,2)	55 (12,5)	
• Lower extremity	3 (1,4)	44 (10,0)	
• Upper extremity / hips / pelvis	4 (1,9)	8 (1,8)	
• Other (combinations of) fractures	5 (2,2)	18 (4,2)	
Fracture type hip and pelvis, n (%)[#^]			**< 0,01** [3]
• Medial collum	107 (52,5)	155 (47,1)	
• Petr. Femur	85 (41,7)	122 (37,1)	
• Subt. Femur	6 (2,9)	11 (3,3)	
• OS pubis ramus inf./OS pubis ramus sup.	1 (0,5)	19 (5,8)	
• Other	5 (2,4)	22 (6,7)	
Treatment type hip and pelvis, n (%)^			0,30 [3]
• IM Pen hip	113 (41,2)	71 (38,4)	
• Hemi arthro plastic hip	80 (29,2)	69 (37,3)	
• Plate osteo synthesis hip	54 (19,7)	32 (17,3)	
• Other	27 (9,9)	13 (7,0)	
Fracture type lower extremity, n (%)[#^]			0,87 [3]
• Ankle	2 (66,7)	22 (40,7)	
• Femurshaft	1 (33,3)	5 (9,3)	
• Other	0 (0,0)	27 (50)	
Treatment type lower extremity, n (%)^			**< 0,01** [3]
• IM pen femur	34 (91,9)	43 (48,3)	
• Plate / screw osteo synthesis ankle	2 (5,4)	15 (16,9)	
• Cast	0 (0,0)	9 (10,1)	
• Other	1 (2,7)	22 (24,7)	
Fracture type upper extremity, n (%)[#^]			0,65 [3]
• Distal radius / ulna	2 (28,6)	17 (37,0)	
• Proximal humerus	3 (42,9)	21 (45,7)	
• Other	2 (28,5)	8 (17,3)	
Treatment type upper extremity, n (%)^			0,35 [3]
• Plate wrist	1 (9,1)	9 (14,3)	
• Plate proximal humerus	1 (9,1)	9 (14,3)	
• Sling	2 (18,2)	8 (12,7)	
• Sling / other	0 (0,0)	8 (12,7)	
• Other	7 (63,6)	29 (46,0)	

+ N = 606, with n = 211 for the group with haloperidol prophylaxis and n = 395 for the group without haloperidol prophylaxis

~ N = 309, with n = 114 for the group with haloperidol prophylaxis and n = 195 for the group without haloperidol prophylaxis

The N of fracture types, hip, lower- and upper extremity, does not correspond with the N of the fracture group due to the combinations of fractures in the fracture group.

^ The N of the fracture type does not correspond with the N of the treatment type of the same fracture type, due to missing values in the data.

[1] Chi square test

[2] Independent t-test

[3] Fisher exact test

Efficacy of the patient groups on the incidence of delirium

The incidence of delirium for the group with haloperidol prophylaxis was 51,9%. For the group without haloperidol prophylaxis the incidence was 8,9%. This was a significant difference ($p < 0,001$) with a relative risk of 5,84 and a 95% CI that lies between 4,21 – 8,09. Patients in the group with haloperidol prophylaxis had a higher risk to develop a delirium than the patients in the group without haloperidol prophylaxis. For each year separately similar results are found (table 5).

Table 5. Efficacy of the group with haloperidol prophylaxis versus the group without haloperidol prophylaxis

	Group with haloperidol prophylaxis (n = 216)	*Group without haloperidol prophylaxis (n = 439)*	*P - value*	*RR (95% CI) or mean difference (95% CI)*
Incidence of delirium, n (%)	112 (51,9)	39 (8,9)	**< 0,001** [1]	5,84 (4,21 – 8,09)
• *Year 2008 (n = 115)*	*27 (44,3)*	*10 (18,5)*	***< 0,01***	*2,39 (1,28 – 4,47)*
• *Year 2009 (n = 141)*	*31 (53,4)*	*11 (13,3)*	***< 0,001***	*4,03 (2,21 – 7,35)*
• *Year 2010 (n = 219)*	*38 (54,3)*	*5 (3,4)*	***< 0,001***	*16,17 (6,66 – 39,32)*
• *Year 2011 (n = 110)*	*10 (47,6)*	*6 (6,7)*	***< 0,001***	*7,06 (2,89 – 17,26)*
• *Year 2012 (n = 70)*	*6 (100,0)*	*7 (10,9)*	***< 0,001***	*9,14 (4,54 – 18,40)*
Length of hospital stay in days, mean (SD)[+]	14,4 (11,2)	12,4 (12,2)	**< 0,05** [2]	2,0 (0,1 – 4,0)
• *Year 2008 (n = 112)*	14,4 (13,3)	*12,6 (10,6)*		
• *Year 2009 (n = 138)*	16,8 (10,9)	*11,2 (6,9)*		
• *Year 2010 (n = 214)*	13,4 (10,6)	*10,9 (12,5)*		
• *Year 2011 (n = 103)*	10,8 (6,5)	*16,3 (17,3)*		
• *Year 2012 (n = 70)*	15,2 (7,1)	*12,0 (8,6)*		
Hospital mortality rate, n (%)	17 (7,9)	15 (3,4)	**< 0,05** [3]	2,30 (1,17 – 4,52)
Complications, n (%)*	127 (58,8)	188 (42,8)	**< 0,001** [1]	1,37 (1,18 – 1,60)

+ N = 637, with n = 214 for the group with haloperidol and n = 423 for the group without haloperidol

* One or more complications

[1] Chi square test

[2] Independent t-test

[3] Fisher's exact test

Influencing factors on the incidence of delirium

As stated in table 5 the group with haloperidol prophylaxis had a higher risk (RR = 5,84 with a 95% CI of 4,21 – 8,09) for developing a delirium than the group without haloperidol prophylaxis. Possible confounders on this relative risk between the group with haloperidol prophylaxis and the group without haloperidol prophylaxis on the incidence of delirium could have been age and gender.

In figure 4 the relationship between age and the incidence of delirium has been shown with Fisher's exact test ($p < 0,001$). For this study the relationship between age and the different groups, group with haloperidol prophylaxis and group without haloperidol prophylaxis, was studied as well. The group with haloperidol prophylaxis compared to the group without haloperidol prophylaxis showed a mean difference in age of 3,5 years. The group with haloperidol prophylaxis had older patients. According to the independent T-test there was a relationship between age and both groups; $p < 0,001$ (mean difference = 3,5; 95% CI: 2,4 – 4,5). Age was a confounder in this study between the group with haloperidol and without haloperidol and the incidence of delirium.

As mentioned in study 1 there was no significant difference between gender and the incidence of delirium, with a relative risk of 0,82 (95% CI: 0,61 – 1,11). There also was no difference between the group with haloperidol prophylaxis and the group without haloperidol prophylaxis regarding gender (RR = 0,85; 95% CI: 0,67 – 1,07). Gender was not likely a confounder in this study between the group with haloperidol and the group without haloperidol and the incidence of delirium.

The crude odds ratio of the group with or without haloperidol prophylaxis on the incidence of delirium was 11,05 (95% CI: 7,23 – 16,87). With a logistic regression model, adjustments were made on the incidence of delirium for the confounders age and gender. Adjusted for gender the OR of the group with haloperidol prophylaxis versus the group without haloperidol prophylaxis on the incidence of delirium was 10,98 (95% CI: 7,19 – 16,77). Adjusted for age the OR of the group with haloperidol prophylaxis versus the group without haloperidol prophylaxis on the incidence of delirium changed to 9,48 (95% CI: 6,17 – 14,59). Adjusted for both age and gender the odds ratio was 9,36 (95% CI: 6,08 – 14,40).

Efficacy of the patient groups on the other outcome measures

The length of hospital stay was longer for the group with haloperidol prophylaxis compared to the group without haloperidol prophylaxis. The mean difference was 2,0 days (95% CI: 0,1– 4,0).
The hospital mortality rate for the group with haloperidol prophylaxis was 7,9% versus 3,4% for the group without haloperidol prophylaxis (RR = 2,30; 95% CI: 1,17 – 4,52). The risk to die during hospitalization was higher for the group with haloperidol prophylaxis than for the group without haloperidol prophylaxis.
The incidence of a complication during hospitalization was for the group with haloperidol prophylaxis 58,8%. For the group without haloperidol prophylaxis the incidence of a complication was 42,8%, which was a significant difference (RR =1,37; 95% CI: 1,18 – 1,60). Patients in the group with haloperidol prophylaxis had a higher risk to develop a complication during their hospital stay than patients in the group without haloperidol prophylaxis.

Patients with surgery

The analyses were further limited to patients that had a surgery during their hospitalization. Of the 655 patients used in this study 530 patients had a surgery. The group with haloperidol prophylaxis (198 patients) showed an incidence of delirium of 51,5% and the group without haloperidol prophylaxis (332 patients) an incidence of 9,6% (RR = 5,35; 95% CI: 3,74 – 7,63). A patient with surgery had a higher risk to develop a delirium in the group with haloperidol prophylaxis than a patient with surgery in the group without haloperidol prophylaxis.

The crude odds ratio of the group with or without haloperidol prophylaxis on the incidence of delirium was 9,96 (95% CI: 6,30 – 15,76). After adjusting for gender the OR of the group with haloperidol prophylaxis versus the group without haloperidol prophylaxis on the incidence of delirium changed to 9,91 (95% CI: 6,26 – 15,69). Adjusted for age the OR of the group with haloperidol prophylaxis versus the group without haloperidol prophylaxis on the incidence of delirium was 8,37 (95% CI: 5,25 – 13,37). Adjusted for both age and gender the OR changed to 8,26 (95% CI: 5,17 – 13,19).

Patients with a hip surgery

The analyses were further limited to patients with a hip surgery. Of the 530 surgery patients, 434 patients had a hip surgery. The group patients with a hip surgery with haloperidol prophylaxis consisted of 178 patients and the group patients with a hip surgery without haloperidol prophylaxis of 256 patients. The incidence of delirium for the group with haloperidol prophylaxis was 52,8% and for the group without haloperidol prophylaxis the incidence was 12,1% (RR = 4,36; 95% CI: 3,05 – 6,24). A patient with a hip surgery that was treated with haloperidol prophylaxis had a higher risk of developing a delirium than a patient treated without haloperidol prophylaxis. Per year the same trend can be noticed; the group with haloperidol had a higher incidence of delirium.

The crude odds ratio of the group with or without haloperidol prophylaxis on the incidence of delirium for hip surgery patients was 8,12 (95% CI: 5,04 – 13,09). After adjusting for gender the OR for the group with or

without haloperidol prophylaxis on the incidence of delirium changed to 8,11 (95% CI: 5,03 – 13,07). Adjusting for age changed the OR to 7,12 (95% CI: 4,38 – 11,58). Adjusted for both gender and age the OR was 7,06 (95% CI: 4,34 – 11,48).

Table 6. Efficacy of the group with haloperidol prophylaxis versus the group without haloperidol prophylaxis for hip surgery patients

	Group with haloperidol prophylaxis (n = 178)	*Group without haloperidol prophylaxis (n = 256)*	*P - value*	*RR (95% CI) or Mean difference (95% CI)*
Incidence of delirium, n (%)	94 (52,8)	31 (12,1)	**< 0,001** [1]	4,36 (3,05 – 6,24)
• *Year 2008 (n = 107)*	*26 (44,1)*	*9 (18,8)*	***< 0,01***	*2,35 (1,22 – 4,53)*
• *Year 2009 (n = 130)*	*28 (52,8)*	*9 (11,7)*	***< 0,001***	*4,52 (2,33 – 8,79)*
• *Year 2010 (n = 113)*	*31 (57,4)*	*5 (8,5)*	***< 0,001***	*6,77 (2,84 – 16,16)*
• *Year 2011 (n = 40)*	*5 (62,5)*	*4 (12,5)*	***< 0,01***	*5,00 (1,73 – 14,66)*
• *Year 2012 (n = 44)*	*4 (100,0)*	*4 (10,0)*	***0,001***	*10,00 (3,95 – 25,34)*
Length of hospital stay in days, mean (SD)[+]	14,7 (11,6)	12,8 (11,6)	0,26 [2]	1,8 (- 0,4 – 4,1)
• *Year 2008 (n = 105)*	14,6 (13,5)	*12,3 (11,0)*	*0,34* [4]	*2,3 (-2,5 – 7,1)*
• *Year 2009 (n = 129)*	17,5 (10,9)	*11,5 (6,7)*	***< 0,01*** [2]	*6,0 (2,6 – 9,3)*
• *Year 2010 (n = 111)*	13,1 (10,6)	*10,2 (4,6)*	*0,58* [2]	*2,9 (-0,2 – 6,0)*
• *Year 2011 (n = 39)*	8,4 (4,6)	*24,2 (24,1)*	***< 0,05*** [2]	*-15,8 (-25,2 – -6,4)*
• *Year 2012 (n = 44)*	12,0 (6,9)	*11,0 (5,7)*	*0,75* [4]	*1,0 (-5,2 – 7,1)*
Hospital mortality rate, n (%)	14 (7,9)	12 (4,7)	0,17 [3]	1,68 (0,80 – 3,54)
Complications, n (%)*	112 (62,9)	134 (52,3)	**< 0,05** [1]	1,20 (1,02 – 1,40)

+ N = 428, with n = 176 for the group with haloperidol and n = 252 for the group without haloperidol

* One or more complications

[1] Chi square test

[2] Mann-Whitney U test

[3] Fisher exact test

[4] Independent t-test

The length of hospital stay was longer for the group with haloperidol prophylaxis compared to the group without haloperidol prophylaxis, with a mean difference of 1,8 days (95% CI: -0,4 – 4,1). The years separately showed the same result, with the exception for the year 2011; in this year the length of hospital stay was longer for the patients without haloperidol prophylaxis.

The hospital mortality rate was for the group with haloperidol prophylaxis 7,9% and for the group without haloperidol prophylaxis 4,7% (RR = 1,68; 95% CI: 0,80 – 3,54).

The incidence of complications was with 62,9% for the group with haloperidol prophylaxis significant different from the group without haloperidol prophylaxis (52,3%). The relative risk was 1,20 with a CI of 1,02 – 1,40. Patients with haloperidol prophylaxis developed more complications than patients without haloperidol prophylaxis.

Patients with more than one visit

In the previous analyses, the treatment policy study and the patient group study, patients that had entered the emergency ward for the first time during the study period were included. It is also interesting to study the patients that entered the emergency ward more than one time during the study period since patients who had developed a delirium during previous hospitalizations are considered at risk for developing another delirium.[19,20]

In total there were 32 patients with more than one visit to the hospital. One patient visited the hospital four times during the selected study period (March 2008 till June 7th 2012), one patient was admitted three times and 30 patients visited the hospital two times. All patients were admitted during the treatment policy with haloperidol prophylaxis except for the patient who was admitted four times; the last admission was during the treatment policy without haloperidol. 11 Patients were given haloperidol prophylaxis or developed a delirium during the first or the second admission. The other 21 patients were not given haloperidol prophylaxis and did not develop a delirium. See table 7 for an overview.

Table 7. Overview of haloperidol prophylaxis use and delirium for patients with multiple admissions

	Admission 1		Admission 2	
Patient	Haloperidol	Delirium	Haloperidol	Delirium
1	x			
2	x		x	
3	x		x	
4	x		x	
5	x		x	x
6	x	x	x	
7	x	x		
8	x	x		
9		x		x
10			x	
11				x
12 - 32				

During the first admission 8 patients were given haloperidol prophylaxis during their admission. Of these 8 patients, 3 patients (37,5%) developed a delirium. 1 Patient developed a delirium without a preventive treatment with haloperidol prophylaxis. During the second admission 6 patients were given haloperidol prophylaxis and 1 patient was diagnosed with delirium (16,7%). Of the 4 patients that developed a delirium during the first admission only 1 was given haloperidol prophylaxis during the second admission (25%). Of the other 3 patients at risk for developing a delirium during the second admission, 1 developed a delirium and the other 2 did not. The patient that developed a delirium during both admissions without haloperidol prophylaxis was a patient of 86 years and had suffered a hip fracture during the first admission and was 87 years with a fracture on the upper extremity during the second admission.

Table 8. Haloperidol prophylaxis use and incidence of delirium among patients with multiple admissions

Haloperidol prophylaxis	**Incidence of delirium**		
	Admission 1	*Admission 2*	*Admission 1 or 2*
Never	4,3%	8,7%	13,0%
Only admission 1	66,7%	0,0%	66,7%
Only admission 2	0,0%	0,0%	0,0%
All admissions	20,0%	20,0%	40,0%

The incidence for patients that were never treated with haloperidol prophylaxis was for the first admission 4,3% ($^{1}/_{24}$) and for the second admission 8,7% ($^{2}/_{23}$). Patients that were only given haloperidol prophylaxis during their first admission had an incidence of 66,7% ($^{2}/_{3}$) for the first admission and 0,0% for the second admission. Patients that were only given haloperidol prophylaxis during their second admission did not develop a delirium during both admissions. Haloperidol prophylaxis during all admissions resulted in an incidence of 20,0% ($^{1}/_{5}$) for admission 1 and admission 2. Combining both admissions, the incidence of delirium was 40,0% for patients that were treated with haloperidol prophylaxis during all admissions and 13,0% for patients that were never treated with haloperidol prophylaxis.

Discussion

This research focused on the efficacy of haloperidol prophylaxis on the prevention of delirium in the Geriatric Fracture Center by studying the treatment policy with and without haloperidol prophylaxis and the patient group with and without haloperidol prophylaxis, primarily on the incidence of delirium and furthermore on length of hospital stay, mortality rate and the complications that occur. The incidence of delirium for the treatment policy with haloperidol prophylaxis compared to the treatment policy without haloperidol prophylaxis was higher for all patients, surgery patients and hip surgery patients. The length of hospital stay was longer and the hospital mortality rate and the complications that occurred were higher for patients in the treatment policy with haloperidol prophylaxis, although not significantly. For the patient group with haloperidol prophylaxis compared to the patient group without haloperidol prophylaxis similar results were found, only with a larger difference between the groups; the patient group with haloperidol prophylaxis had a higher incidence of delirium for all patients, surgery patients and hip surgery patients. For all patients there was a longer length of hospital stay and a higher mortality rate. The incidence of complications that occurred was higher for all patients and hip surgery patients.

The results of the treatment policy study showed a difference between the treatment policy with and without haloperidol prophylaxis for the entire study period on the incidence of delirium. For the treatment policy with haloperidol prophylaxis a decrease in incidence of delirium was found over the years. This was probably due to improved skills of healthcare professionals, which may have led to a better recognition of patients at risk for developing a delirium and providing the necessary care in time. Also, the push and pull system of the CGT could have improved over the years. This push and pull system supports the patient flow in the CGT by setting a target date for when the patient should be discharged from the hospital. This target date supports the treatment policy and the treatment goals for the patient, which could have led to an improvement of the efficiency of the treatment policy. Comparing a fully implemented treatment policy with haloperidol prophylaxis (year 2011) with the treatment policy without haloperidol prophylaxis showed a similar incidence of delirium (14,5% versus 13,3%), which means that both policies can be seen as equal. However, there were much more patients with a hip fracture in the treatment policy with haloperidol prophylaxis (79,2% versus 63,3% for the treatment policy without haloperidol prophylaxis) and these patients have a higher risk for developing a delirium than patients without a hip fracture, which could have influenced the incidence of delirium for the treatment policy with haloperidol prophylaxis. In 2011 there were only a few hip surgery patients, compared to the other years in the treatment policy with haloperidol prophylaxis, which could cause a lower incidence of delirium for the treatment policy with haloperidol prophylaxis for that year (RR = 2,62; 95% CI: 0,77 – 8,94). Therefore the analysis of the hip surgery patients for the entire study period on the incidence of delirium was used to determine the difference between both policies, which gave a relative risk of 3,6 (95% CI: 1,20 – 10,63). Patients of the treatment policy with haloperidol prophylaxis had a higher risk of developing a delirium than patients of the treatment policy without haloperidol prophylaxis. Furthermore, the treatment policy with haloperidol prophylaxis (all patients and hip surgery patients) resulted in a longer hospital stay and more complications occurred in this treatment policy, although not significantly. The overall conclusion of the treatment policy study is that the treatment policy with haloperidol prophylaxis shows less favorable results than the treatment policy without haloperidol prophylaxis.

Comparing the patient group with haloperidol prophylaxis and the patient group without haloperidol prophylaxis in the patient group study is troublesome. At baseline both groups were different on several characteristics. Patients of both groups were different type of patients; patients in the group with haloperidol prophylaxis were most likely more at risk for developing a delirium and had worse health symptoms and were therefore given haloperidol prophylaxis. Patients that were not given haloperidol prophylaxis as a preventive treatment were most likely healthier. For instance, patients of the group with haloperidol prophylaxis are older than the patients in the group without haloperidol prophylaxis with a difference of 3,5 years. With increased

age, the risk of developing a delirium increases as well, which contributed to the differences in patients of both groups.[11] The incidence of delirium was higher for the group with haloperidol prophylaxis than the group without haloperidol prophylaxis for all patients, surgery patients and hip surgery patients. After adjusting for the confounders age and gender the odds ratio for all patients changed with 1,69 to an OR of 9,36 (95% CI: 6,08 – 14,40), however the difference between the group with haloperidol prophylaxis and the group without haloperidol prophylaxis remains. A similar result was found after correcting for age and gender for surgery and hip surgery patients. For all patients the group with haloperidol prophylaxis had a longer length of hospital stay, higher mortality rate and more complications occurred. For hip surgery patients these differences are also found, although not significantly, except for the complications that occur. Overall the conclusion of the group study is that the patient treated with haloperidol prophylaxis shows less favorable results than the patient without haloperidol prophylaxis.

The results of the patient group study can be compared to the results of the first RCT (2005) where the efficacy of haloperidol prophylaxis was studied among elderly hip surgery patients.[15] In both studies the same dosage of haloperidol prophylaxis was given among hip surgery patients. With a RR of 0,91 (95% CI: 0,6 – 1,3) it was shown that haloperidol prophylaxis is not effective in preventing delirium for the haloperidol prophylaxis group of the RCT. Comparing this result to the hip surgery patients of the group study of this research, the differences in study design should be taken into account. This current study was not randomized and the baseline characteristics were not similar for the group with haloperidol prophylaxis and the group without haloperidol prophylaxis. The RR of this study was 4,36 (95% CI: 3,05 – 6,24) which states that the group with haloperidol prophylaxis had a higher risk for developing a delirium and therefore haloperidol prophylaxis is not effective in preventing delirium. Both studies had as outcome that haloperidol prophylaxis is not effective in preventing delirium, only this study states that patients with haloperidol prophylaxis have a higher risk for developing a delirium, whereas the RCT showed a similar risk between the group with haloperidol prophylaxis and the group without haloperidol prophylaxis. The other RCT (2012) had a different patient population and cannot be compared to the results of the group study.[12]

The analysis about patients with more than one visit during the study period showed an interesting result. During the time that the treatment policy with haloperidol prophylaxis was implemented, the healthcare professionals did not follow their own policy. In 75% of the cases a patient suffered a delirium during the first hospitalization and was not treated with haloperidol during the second admission. Especially patients that have developed a delirium during earlier admissions are considered being at risk for developing a delirium. They should have been treated with haloperidol prophylaxis according to the treatment policy with haloperidol prophylaxis of the CGT. Furthermore, the incidence of delirium was higher for patients that were given haloperidol prophylaxis during all admissions than for patients that were never treated with haloperidol prophylaxis. The underlying cause for not following the implemented policy could be that the healthcare professional has difficulty understanding the treatment policy of the CGT, which causes problems for the proper implementation of the policy.[21]

Before the final conclusion of this study can be given, the strengths and limitations of this research should be mentioned. A strong point of this research is that the research contributes to the information about the efficacy of haloperidol prophylaxis for elderly patients with a fracture on the incidence of delirium. At this moment there are only two RCTs available regarding this topic with different results, which could imply that healthcare professionals should not just assume that haloperidol prophylaxis is the antipsychotic drug to prevent delirium.[11,15] This study contributes to the knowledge about the efficacy of haloperidol prophylaxis on the incidence of delirium with two different studies, which raises more questions regarding this topic.

More research about the efficacy of haloperidol prophylaxis on the incidence of delirium is necessary, since this study also has some limitations. The most important limitation in this study is the fact that only adjustments for the confounders age and gender could be made. According to the literature, other risk factors for a delirium

are dementia, co-morbidity, visual or hearing impairment, alcohol abuse, drug use and depression.[22] In this study these risk factors are not recorded and could therefore not be studied. Therefore it remains uncertain what the efficacy of haloperidol prophylaxis is since a delirium could be caused by these risk factors instead of haloperidol prophylaxis. Especially for the patient group study not being able to correct for the risk factors is a problem, since these patients already differ on several characteristics at baseline. Patients at risk for developing a delirium were given haloperidol prophylaxis, which could mean that the patient group with haloperidol prophylaxis consisted of more patients with a worse health state than the patients in the group without haloperidol prophylaxis. Adjusting for this health state difference was impossible, which causes more limitations for the patient group study than for the treatment policy study. In the treatment policy study, both policies consisted of patients who were at risk for developing a delirium. A reason for the differences at baseline in the patient group study is that the patients were not randomized in this study. Randomization would have prevented this difference and would give a clearer result of the efficacy of haloperidol on the prevention of delirium.
Furthermore, for the treatment policy with haloperidol prophylaxis an assumption was made; this treatment policy remained the same over the years and could therefore not have an effect on the incidence of delirium and the other outcomes. If this assumption was false and the treatment policy did change, it could have had an influence on the results of this study.

Not only does this research contribute to the topic of haloperidol prophylaxis and the incidence of delirium in general, it also is of value for the ZGT. It gives the ZGT an overview of the efficacy of haloperidol prophylaxis for both treatment policies as well as both patient groups. This study also gives the ZGT insight in the completeness and accuracy of their database, which shows limitations. This could be caused by the retrospective design of this study.[24] The reason for collecting data retrospectively was that the ZGT already changed their treatment policy with haloperidol prophylaxis to the treatment policy without haloperidol prophylaxis before this study started.

Only two of the four databases of Thinkwise (fractures and complications) could be used in this study. The other two databases, advice and analysis, recorded interesting information which could have been helpful for this research. For example about dementia, some lab functions and medication use of the patient. For future research regarding this topic it is wise to use these databases as well or develop a new database where all risk factors of delirium are recorded.
Apart from the risk factors that were not recorded, there are missing values in the data that was recorded. Two months of the year 2011 are not used in this study (May and June) due to a transition of the Rochester database to Thinkwise. The data of these months is available and should be implemented in future research. Furthermore, per patient different types of data was missing, which is the reason why the patients characteristics do not always display the same amount of patients when one would expect the same amount of patients. For instance the amount of patients with fracture type hip does not correspond one on one with the treatment type of the hip fracture patients. For future research it would be recommendable if all known data of a patient is submitted in the database. Due to missing values, assumptions were made about the incidence of delirium and the haloperidol use. Assumed was that for the missing values no delirium occurred or no haloperidol prophylaxis was given. Around 14,5% (95 patients) of the data about delirium was missing. A small study in the digital patient files of 50 patients resulted in 3 patients that have developed a delirium according to their medical file. If this small study would be representative for the 95 missing patients, the incidence of delirium would be slightly different without missing values, but neglectable. For the haloperidol prophylaxis use 22,6% of the information was missing, which could change the distribution of the group study if all information was present and no assumptions had to be made.
Besides the missing values there were also errors in the database. Only a few patients were excluded from this study due to errors, however more errors in the data of patients that remained in the study have been found; especially errors regarding dates. Entering a date in Thinkwise is done manually which is likely to cause the

errors. When options are available for entering the day, month and year, less errors are made by the healthcare professional entering the data in the database.[23]

It is recommended that the ZGT should study the efficacy of other medications regarding the prevention of delirium. A recent study shows that other medications, atypical antipsychotics, are as effective as haloperidol in the management of delirium and show fewer extra pyramidal symptoms. This could mean that a good alternative for haloperidol is found for the treatment of delirium, and perhaps also for the prevention of delirium.[25] In a recent RCT melatonin was studied. It was found that patients administered with melatonin show a significantly lower rate of delirium that patients without melatonin (adjusted OR = 0,19; 95% CI: 0,06 – 0,62).[26,27] Also interesting for the ZGT is to look further than pharmacological preventions. Non pharmacological interventions include training and education programs for health care staff, improvement of the environment of the patient, proactive geriatric consultation, nutritional support, infection control measures and protocols to prevent delirium, like the NICE guideline for delirium.[15,28] Non-pharmacological measures show also interesting results on the prevention of delirium.[2,29] A recent study shows that a non-pharmacological intervention with family members is effective in preventing delirium (RR = 0,41; 95% CI: 0,19 – 0,92).[30] The family helped the patient with the reorientation in the hospital and was allowed to visit the patient for 5 hours a day. Besides the help of family members, the patients room in the hospital was surrounded with familiar things, for instance a blanket or a photo.

Whether changing the treatment policy with haloperidol prophylaxis to the treatment policy without haloperidol prophylaxis was the right decision for the ZGT remains uncertain. The results of this study, both treatment policy study and patient group study, support the decision to change the treatment policy. The results of the first RCT (2005) could also support this decision, since similar results were found between the group with haloperidol prophylaxis and the group without haloperidol prophylaxis. However, the limitations of this study have to be taken into account. The main limitation is not correcting for other risk factors besides age and gender. Since there are many risk factors that could have influence on the incidence of delirium, it remains unclear what the efficacy of haloperidol on the incidence of delirium is. More randomized research is necessary regarding haloperidol prophylaxis. Healthcare professionals should not assume that haloperidol is the antipsychotic drug to prevent a delirium. Other options, pharmacological or non-pharmacological, are worth investigating as well.

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