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EDITORIAL

Big hits in *the Netherlands Journal of Medicine*

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For some years now articles in *the Netherlands Journal of Medicine* are indexed in PubMed and easily accessible via the publisher's website. This important step has made contributions in *the Netherlands Journal of Medicine* much more visible for a worldwide readership and greatly contributes to the standing of the Journal. It may be speculated that a considerable part of the increase in the impact factor of the Journal that we have witnessed in recent years is due to this situation.[1] For journals the impact factor is an important measure of how relevant their published papers are for the medical scientific community. In addition, the number of 'hits' on the Journal's website, leading to the download of the paper, is another and maybe equally significant factor.

Over the last 12 months about 50,000 hits were counted on the website of *the Netherlands Journal of Medicine*. When we analyse the number of hits in the last year immediately after their publication in *the Netherlands Journal of Medicine*, a number of interesting conclusions can be drawn. First, and not surprisingly, the cumulative number of hits escalates over time as an increasing number of people discover and download the article (*figure 1*). However, this is not true for all papers as in particular photo quizzes enjoy an immediate attention that remains quite stable over time. Best-viewed articles in *the Netherlands Journal of Medicine* are reviews and editorials. *Table 1* reports on the mean number of hits of each of the sections in the Journal and provides a similar picture. The four reviews that were the biggest hits for the Journal in the last three years were all downloaded more than 1000 times in the first year after publication.[2-5] Original articles are also frequently downloaded but here the variation is somewhat higher. The most viewed papers in the last year had about 600 hits.[6-8] The number of downloads for case reports is about the same but relatively quite high for this type of article.[9] The winning papers in this category had 550 hits or more.[10,11] Photo quizzes have a rather stable download rate of about 400 but some of them are very popular with more than 700 downloads.[12-14]

Figure 1. *Number of hits over one year after publication of articles in the Netherlands Journal of Medicine for each of the journal sections*

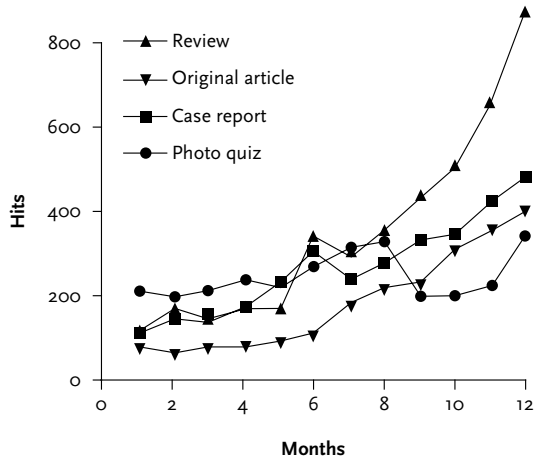
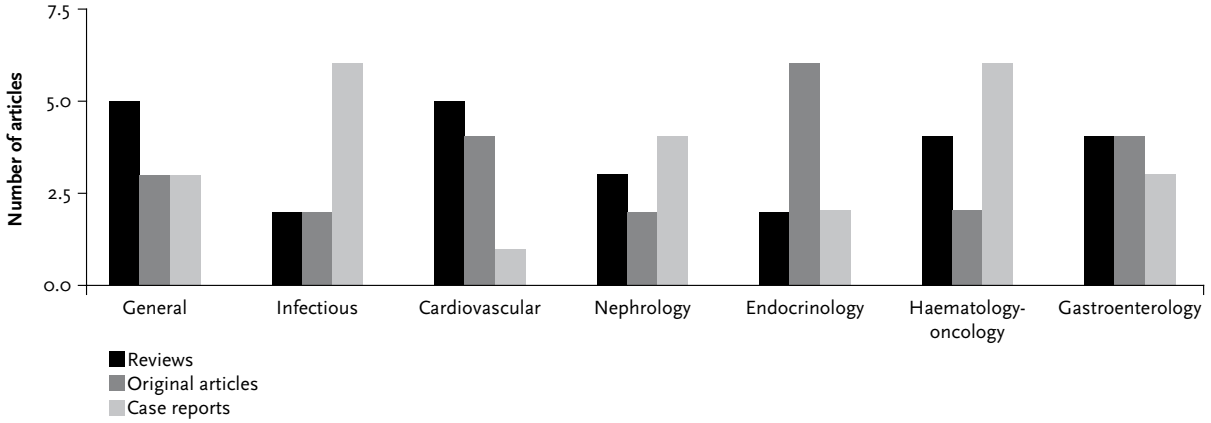


Table 1. *Mean number of hits per year for each section of the Netherlands Journal of Medicine, with maximum and minimum per category*

	Editorials n=11	Reviews n=17	Original articles n=20	Case reports n=27	Photo quizzes n=22
Mean (± SD) number of hits/year	529 (± 129)	789 (± 103)	402 (± 221)	445 (± 187)	415 (± 87)
Maximum	941	1034	604	578	785
Minimum	179	134	175	144	235

Figure 2. *Distribution of articles in the Netherlands Journal of Medicine over the various subdisciplines of medicine*



It is also interesting to analyse which subdiscipline of medicine the articles in *the Netherlands Journal of Medicine* come from. *Figure 2* shows the origin of the papers for each of the article categories. In general, the most important areas of medicine are all covered in the various journal sections. Relatively speaking, cardiovascular medicine seems somewhat underrepresented in case reports, whereas infectious diseases and haematology/oncology are slightly overrepresented; however, the numbers are relatively small. When further analysing the relationship between the subdisciplines and the number of hits, there is no significant difference between the number of downloads and the subdiscipline of the paper, although there seems to be a trend that papers in general medicine or cardiovascular medicine are somewhat more frequently downloaded.

It would be interesting to establish a relationship between the number of downloads on the website and the number of 'official' citations an article receives. We are in the process of analysing that relationship as it may represent a new and easy to establish measure of the impact a specific paper may have. We hope that we will be able to report on this in one of the next issues of *the Netherlands Journal of Medicine*.

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REVIEW

Should antiretroviral therapy for HIV infection be tailored for intracerebral penetration?

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ABSTRACT

The continuous replication of HIV-1 in the central nervous system, in particular the brain, and its potential long-term deleterious effect is the focus of this review. Cognitive deficits are observed in a significant percentage of HIV-1-infected patients. That may occur despite successful peripheral suppression of the HIV-1 replication. Compartmentalisation of HIV-1 in the brain, genetic mutation of HIV-1, age, HCV coinfection and poor intracerebral penetration, as well as possibly a direct toxic effect of antiretroviral drugs, are factors that may account for potential creeping damage of the brain after many years of treatment. Patients with neurological symptoms or cognitive deficits may require another approach to the treatment of their HIV infection.

KEYWORDS

Antiretroviral drug, central nervous system, HIV, penetration

INTRODUCTION

The central nervous system (CNS) is a major target of HIV-1 infection and HIV-1-related diseases.[1,2] Chronic HIV-1 infection of the CNS begins during primary infection and continues in nearly all untreated seropositive individuals. Late during the course of systemic infection, asymptomatic and seemingly benign CNS disease can progress to more severe disease. The clinical presentation is heterogeneous and can include a syndrome of cognitive, motor, and behavioural dysfunction formerly known as AIDS dementia complex (ADC), now called HIV-associated dementia (HAD). Less serious stages are nowadays included in the collective term, HIV-associated neurocognitive disorders (HAND).[3] In the late stages of immune suppression, the CNS is also vulnerable to opportunistic infections. This review will focus on the effects of HIV-1 infection on the CNS as well as the effects of combination antiretroviral therapy (ART) and its limitations with respect to the CNS. Consideration will be given to whether chronic infection in treated individuals has long-term neurological sequelae and, if so, whether they can be treated or even prevented.

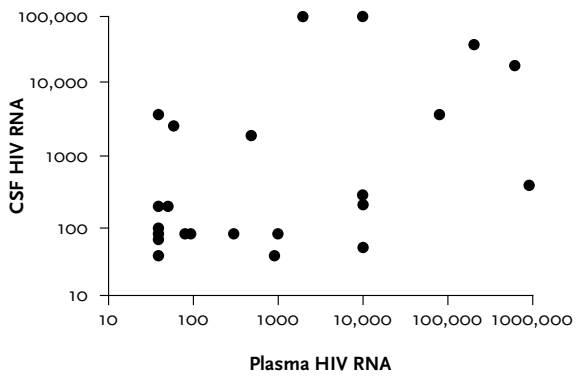
OVERALL IMPACT OF ART ON AIDS-RELATED NEUROLOGICAL DISEASES

Combination ART has substantially influenced HIV-induced CNS disease. The incidence of all AIDS-related CNS diseases is now markedly reduced, at least in developed countries. This was well documented in the EuroSIDA cohort study, which showed a tenfold decrease in CNS diseases that paralleled a decrease in systemic AIDS-related complications after combination ART was introduced.[4] HAD was the most common severe CNS disease before the introduction of ART, and showed the greatest reduction in incidence between 1994 and 2002.[4]

Zidovudine was the first antiretroviral drug with therapeutic benefit on the course of HAD. But since an early AIDS Clinical Trials Group (ACTG) study (protocol 005) showed this effect,[5] few controlled treatment trials with other antiretroviral drugs have been performed. Although ART can clearly arrest HAD and reverse its neurological disability, the general magnitude of this

effect is variable and not precisely defined. Low CD4 counts were an important risk factor for HAD in the era before combination ART, and continue to be so in the modern treatment era, also for the development of HAND.[6] Additional risk factors for new or progressive HAND in the modern treatment era include incomplete immune recovery, rapid immune recovery with immune recovery inflammatory syndrome (IRIS),[7] hepatitis C virus (HCV) coinfection,[8-10] and advancing age.[11] The aggregate experience that ART primarily ameliorates HAND, however, appears to be compelling, and indicates that neurological dysfunction can be reversed.[11-14]

Figure 1. *Plasma and CSF HIV RNA concentrations in 31 HIV-1 seropositive patients*



Plasma and CSF samples were taken at the same day with a maximal time span of one hour.
Source: Radboud University Medical Center, Department of General Internal Medicine, Nijmegen, the Netherlands.

CHRONIC CNS HIV-1 INFECTION: VIROLOGICAL AND BIOCHEMICAL ASPECTS AND ITS CLINICAL IMPACT

In the absence of treatment, HIV replication in cells of the nervous system is a nearly constant component of HIV-1 infection and has been characterised most clearly by studies analysing cerebrospinal fluid (CSF). During life, it is not possible to measure HIV replication in the brain. Therefore, HIV RNA levels in the CSF together with markers of inflammation and neuropsychological tests are considered to give guidance on the degree of brain damage during the course of HIV-1 infection.[15-17]

HIV-1 RNA can be detected in the CSF of nearly all those with infection, from the period of initial viraemia through the course of neurologically asymptomatic infection and in those developing HAND.[15-18] A number of studies have shown that HIV-1 RNA in CSF is nearly ubiquitous but variable in its magnitude and in its relation to HIV-1 RNA level in blood.[15-21] Generally, in untreated individuals, CSF HIV-1 RNA levels are approximately tenfold lower than plasma HIV-1 RNA levels, but the difference between viral concentrations in the two fluids varies considerably with levels in CSF exceeding those in blood in some individuals. An example of the relationship between HIV RNA levels in CSF and blood is shown in *figure 1*. In general, HIV RNA levels in CSF correlate with those in blood although this correlation weakens in those who have advanced HIV disease or who have HAND.[18] In addition to quantitative differences between CSF and blood, viral populations that are found in the nervous system can also diverge qualitatively from those in blood. Genetic compartmentalisation of HIV-1 has been demonstrated by several studies.[22-27] During acute infection, HIV-1 populations in CSF and blood are probably monophyletic, but then, during chronic infection, the populations expand and diverge, with the greatest divergence in patients who have HAND. Functional compartmentalisation has also been shown with respect to drug resistance, use of entry receptors, and cell tropism. Differences in drug susceptibility between CSF and blood HIV-1 populations have also been reported.[28-31] Although viral replication in CSF in the presence of sub-therapeutic drug concentrations might enhance the selection of resistance mutations, few studies have carefully compared drug concentrations in CSF with the development of drug resistance.[32] Recent findings on the adaptations of HIV-1 to neural cells[33-35] have advanced our understanding of HIV-1 neuroadaptation and neurovirulence but additional work is needed to understand, for instance, the clinical implications of these and other findings.

CSF analysis also indicates that HIV-1 infection is associated with chronic immune activation in the nervous system (neuroinflammation, as indicated by frequent, although usually mild, CSF pleocytosis and elevated levels of several soluble immunological markers[19,36-38] e.g. neopterin, β-2-microglobulin, quinolinic acid, and CCL2/MCP-1. The persistence of HIV-1 and the associated neuroinflammation raise the important question of whether chronic asymptomatic infection is accompanied by ongoing, low-grade brain injury despite the lack of overt symptoms and signs. If this chronic inflammatory[37] state leads to brain injury, will survivors develop neurological impairment years later despite otherwise effective therapy? Several studies have reported neurocognitive impairment in HIV-infected patients, typically with a detrimental impact on activities of daily living (ADLs).[1,4-43] Indeed, diminished group performance has led to the inclusion of the designation 'HIV-associated asymptomatic neurological impairment' (ANI) as a diagnosis subsumed in the HAND classification approach.[3] The other diagnoses that comprise HAND are 'mild neurocognitive disorder', a milder symptomatic syndrome that clearly impacts ADLs, and 'HIV-associated dementia', a more severe, symptomatic

syndrome that markedly impacts ADLs. Neurocognitive impairment may persist despite successful treatment with antiretroviral therapy.[42,43] Therefore combination ART for HIV-1 infection may incompletely treat the CNS.

Influence of ART on CSF HIV RNA

In general, HIV-1 in CSF responds very well to ART;[44-51] as HIV-1 RNA levels in plasma become undetectable, so do those in CSF in nearly all individuals. However, the relative rates of viral decay in the two compartments may differ in some, with HIV-1 RNA concentrations falling more slowly in CSF than in plasma. Slower decay has been noted in subjects with HAD and lower blood CD4 cell counts but without CSF pleocytosis.[50-53] These observations can be interpreted as being consistent with a simple model of compartmentalised CSF HIV-1 infection, with the lag in viral response in CSF due to slow cell turnover and consequent prolonged virion production by brain macrophages, reduced trafficking of shorter-lived lymphocytes into the CSF from blood, and lower drug concentrations in the CNS. Drug penetration in the CNS largely depends on the physicochemical properties e.g. protein binding, molecule size, lipophilicity, or use of membrane transporters in the blood brain barrier such as P-glycoprotein. In addition drug penetration into the CNS also can be modified.[54-56] Considerable differences exist between antiretroviral drugs with respect to penetration into the CNS. Letendre *et al*.[56] have proposed a simple scheme for grouping drugs by CSF penetration ability based on drug properties and clinical studies, rating them as 0 (lower penetration), 0.5 (intermediate penetration), or 1 (higher penetration). No drug concentrations in CSF have yet been published for newer antiretroviral drugs such as darunavir, etravirine, raltegravir, and maraviroc.

Although potentially useful as a guide for selecting treatment, several observations suggest that the model may not fully account for treatment effects in all settings. For example, it may not explain the overall effectiveness of a wide variety of drug regimens in the suppression of CSF HIV-1 RNA levels or why cases of high CSF virus levels in the presence of suppressed plasma virus levels are rare. The very rapid decay of HIV-1 in CSF is equivalent to that of plasma virus in some subjects, which may reflect increased permeability of the blood-brain barrier or high levels of pretreatment lymphocyte trafficking. Such inter-individual differences may reflect differences in genetic traits, such as expression of chemokine receptors and adhesion molecules, or in comorbidities, such as recreational drug use and HCV coinfection. Also it should be stressed that potency of the complete (usually three drug) regimen and to what extent concentrations exceed the IC90 are more relevant than single drug concentrations in the CSF. This and the issues mentioned above are areas for ongoing and future research.

Table 1. *Categorisation of antiretroviral drugs by estimated neuroeffectiveness (CNS penetration-effectiveness rank)*

	Better	Intermediate	Worse
NRTIs	Abacavir	Emtricitabine	Didanosine
	Zidovudine	Lamivudine	Tenofovir
		Stavudine	Zalcitabine
NNRTIs	Delavirdine	Efavirenz	
	Nevirapine		
PIs	Amprenavir-r	Amprenavir	Nelfinavir
	Indinavir-r	Atazanavir	Ritonavir
	Lopinavir-r	Atazanavir-r	Saquinavir
		Indinavir	Saquinavir-r
			Tipranavir-r
Fusion inhibitors			Enfuvirtide

-r = drugs boosted by ritonavir. Source: Dr S. Letendre.

CNS SIDE EFFECTS OF HAART

To date, the most widely recognised antiretroviral with CNS side effects is the non-nucleoside reverse transcriptase inhibitor efavirenz.[57] Vivid and dysphoric dreams, in particular during the first weeks of treatment, are commonly reported symptoms. Less than 10% discontinue treatment because of these symptoms. Prospective studies have not found a clear deleterious effect of efavirenz on longer term neuropsychological performance or on depressive scores,[58,59] although the findings are not entirely consistent.[60] The mechanism of these symptoms is not well understood, although they seem to be linked with higher levels of drug exposure.[61,62] So far, no conclusive data show that other antiretroviral drugs have a direct toxic effect on the brain. However, some animal and human data on a potential deleterious effect of NRTI on brain mitochondria and cellular metabolism do exist.[63] In addition there is some concern that drug-induced injury of mitochondria or changes in lipid metabolism, for example, may injure the brain, particularly in more vulnerable hosts (e.g., older individuals).

ANTIRETROVIRAL THERAPY AND NEUROCOGNITIVE PERFORMANCE

Would initiation of ART earlier in the course of HIV disease further reduce the risk of development of HAND? Hitherto, should treatment with neuroeffective antiretroviral drugs be recommended in all individuals at the time of treatment initiation?[64] These questions cannot yet be confidently answered. Many issues should be taken into account in the treatment of HIV disease: in the first

place potency, then toxicity, and also dosing simplicity. The literature on the effects of ART on neurocognitive performance is not entirely consistent. Case reports show improvement of symptoms of dementia that paralleled improvement of HIV RNA levels and the inflammatory markers in the CSF.[67,68] Some research studies identified that more neuroeffective regimens were associated with greater improvement[65,66] but others did not.[69,70] Important methodological differences between these studies exist including the approach to testing, the method of estimating neuroeffectiveness, the types of regimens used, and the demographic and disease characteristics of the study population. Importantly, improvement in neurocognitive performance is a secondary effect of control of HIV replication, which is the primary effect of ART. Control of HIV in the CNS is a necessary but not necessarily sufficient condition for neurocognitive protection or improvement. For all these reasons, caution must be exercised in interpretation of these research findings. Additional clinical trials to address the question whether ART regimens should be optimised for neuroeffectiveness are not easily performed but at least one is underway.[71] Another important question for future clinical trials to address is the use of adjuvant therapies to improve intracerebral penetration.[72-75]

Given these uncertainties, how should treatment be tailored to the nervous system now? This question cannot easily be answered. The existing data so far indicate that in neurologically asymptomatic patients – that is, in most of those who initiate therapy – the CNS likely warrants no special consideration. However, in patients who have HAND, a different approach could be advocated. In these patients treatment could be initiated with a regimen that penetrates well into the CSF and into the brain. The effect then could be monitored by measurement of HIV RNA and drug levels in CSF as well as repeated neuropsychological tests.

CONCLUSIONS

Although a number of important treatment issues have not yet been addressed, the advent of ART has had a profound impact on severe CNS disease as a complication of HIV-1 infection. This impact includes a marked reduction in the incidence of major CNS opportunistic infections and HAD, and effective treatment for patients presenting with new-onset HAND. With this success, attention has turned to other aspects of CNS HIV-1 infection and particularly to the question of the optimal management of milder, but still clinically relevant, HAND syndromes. CNS HIV-1 infection and the associated neuroinflammation may damage the brain during the long period before treatment is initiated and may even continue in the presence of effective systemic viral suppression. Now that the most conspicuous and severe neurological complications of HIV-1 infection can be avoided in most cases, the effects of therapy on the remaining clinical syndromes of brain injury must be carefully considered and explored.

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REVIEW

A systematic review on the influence of trial quality on the effect of garlic on blood pressure

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ABSTRACT

Background: Garlic is a widely used herbal product for hypertension. Previous meta-analyses on the effect of garlic on blood pressure (BP) have been contradictory however. We hypothesised that methodological deficiencies may have contributed to this disagreement. We therefore evaluated whether trials reporting on the effect of garlic on BP had sufficient methodological qualities and a proper description of BP determination.

Methods: MEDLINE, EMBASE, AMED, the COCHRANE library, IBIDS and CINAHL were systematically searched for trials reporting on the effect of garlic on BP. Both the methodological quality and the quality of blood pressure measurement were appraised using predefined quality scores.

Results: 32 Studies were identified. Of these studies, 13 were included previously by other meta-analyses. The methodological quality of the studies was poor. Only four trials had adequate allocation concealment, no single trial reported an intention-to-treat analysis and blinding of the evaluators was done in three trials only. Moreover, half of the studies did not report any data on BP measurement. No trials reported on the arm level. Body position was described most often. All trials fulfilling a predefined cutoff point were conducted in normotensive subjects.

Conclusion: The effect of garlic on blood pressure cannot be ascertained. Previous meta-analyses have been based on trials with inadequate study designs, methodological deficiencies and with too little information about blood pressure measurement. In our view, use of garlic cannot be recommended as antihypertensive advice for hypertensive patients in daily practice.

KEYWORDS

Blood pressure, hypertension, garlic, systematic review, quality analysis

INTRODUCTION

For the treatment of hypertension, non-pharmacological therapeutic advice is the initial therapeutic approach in patients with an increased cardiovascular risk.[1] A number of such lifestyle recommendations clearly reduce blood pressure, e.g. weight reduction and regular physical activity.[1] Food supplementation could provide another, less strenuous non-pharmacological intervention.

Garlic is the second most used herb taken by patients with cardiovascular disease.[2] Moreover, garlic might lower blood pressure via the conversion of garlic-derived organic polysulphides into hydrogen sulphide by the red blood cell leading to vasorelaxation.[3] It could therefore be a potential target as an antihypertensive food supplement.

Indeed, several trials suggest possible short-term effects of garlic on cardiovascular risk factors.[4] The effects of garlic on blood pressure specifically have been summarised in three systematic reviews.[4-6] However, the results were contradictory. This phenomenon has been evaluated previously by Linde *et al.*[7] In their analysis on discordant conclusions of systematic reviews in complementary medicine, they concluded that these differences were mostly due to differences in inclusion and exclusion criteria. We wondered whether this could also be explained by the different approaches to appraise trial quality,[8] because trials in complementary medicine have low methodological quality[9] and because these deficiencies may translate into biased findings in systematic reviews.[10]

Besides, none of these reviews[4-6] looked at the quality of blood pressure measurement. Recently, Wood *et al.* demonstrated that bias in intervention effects is only seen in trials using subjective outcomes, i.e. physician assessed disease outcome.[11] During blood pressure measurements many errors can occur resulting in varying blood pressures making it amenable to faulty outcomes.[12] Thus when addressing the bias in blood pressure trials introduced by methodological deficiencies, proper blood pressure measurements seem to be an additional quality criterion.
We therefore conducted an analysis of the methodological quality of trials reporting on the effect of garlic on blood pressure using multiple strict quality criteria. The present study aims to answer the following four questions:

- Does garlic lower blood pressure in humans?
- What is the methodological quality of human trials measuring the effect of garlic on blood pressure?
- What information about criteria for blood pressure measurements is presented in these garlic studies?
- Did the inclusion of methodologically poor studies affect the conclusions of previous systematic reviews?

METHODS

Literature search

MEDLINE (1966-2008), EMBASE (1980-2008), CINAHL (1982-2008), IBIDS (2008), AMED (1985-2008) and the COCHRANE library were searched from March 2008 until May 2008 using search strategies mentioned in *table 1*. The search was last updated in January 2009 by two reviewers independently. References from garlic reviews and eligible trials were searched for additional articles.

Selection criteria

Studies in adults measuring the effect of garlic on blood pressure were considered eligible. Inclusion was limited to studies lasting more than eight weeks and with more than 20 participants. In crossover trials each parallel arm had to last more than eight weeks. Trials were selected independently by two reviewers on the basis of abstracts.

Data extraction

Two reviewers identified eligible trials. Data extraction and quality assessment were done by two reviewers. When results of a scoring card (see: quality analysis) deviated more than one point, a third independent reviewer was consulted. Differences were resolved by consensus. In case of different conclusions, consensus could always be reached.

Quality analysis

Both the methodological quality and the quality of blood pressure measurement were assessed using two different scoring systems.
Methodological quality was assessed using a scoring card derived from the Cochrane checklist 'the assessment of a randomised trial'.[13] The card consisted of nine items mentioned in *table 2*. A trial had to describe each item specifically. Moreover, both the number as well as the reasons for dropping out had to be recorded. Trial arms had to be similar in age, sex, blood pressure and modifying factors (smoking, diabetes, hypercholesterolaemia, overweight, alcohol, cardiovascular comorbidity; at least four mentioned). Each study could score a maximum of nine points.

Table 2. *Methodological quality of the selected trials (n=32) using the nine quality criteria*[*]

Cochrane criterion	Number of studies fulfilling criterion
Allocation concealment	4
Randomisation	28
Patients blinded	24
Researchers blinded	24
Evaluators blinded	3
Comparable groups	10
Adequate lost-to-follow-up analysis	15
Intention-to-treat analysis	0
Groups receiving same treatment	27

[*]**Dutch Cochrane Centre: checklist for bias assessing of randomised controlled trials. www.cochrane.nl. Accessed 21 July 2008.**

Table 1. *Search strategy for each search engine*

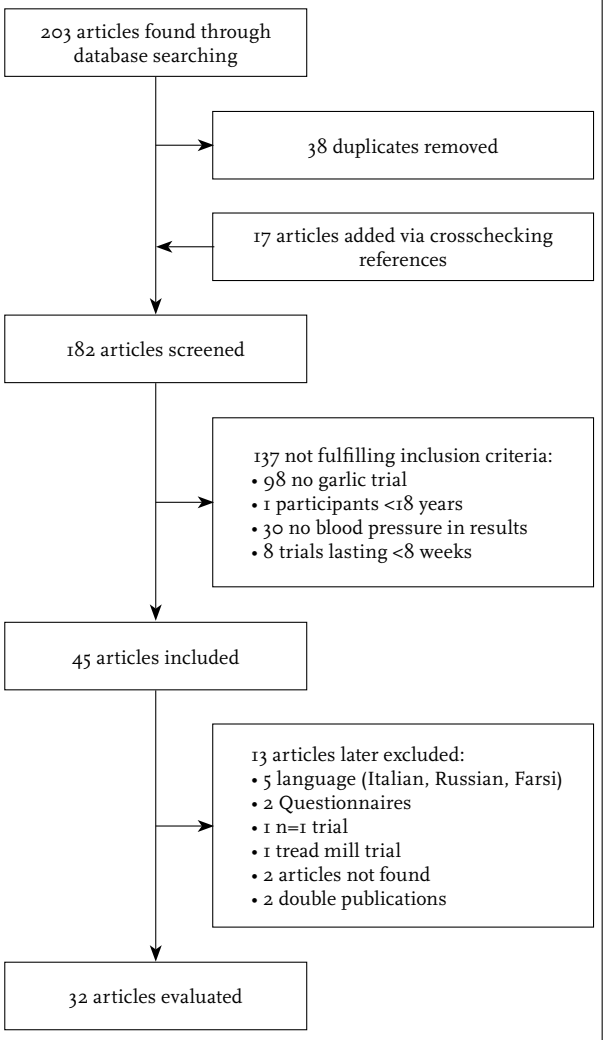
Medline	((((blood pressure) OR (blood pressure determination) OR (hypertension)) OR ('Blood Pressure Determination'^{Mesh} OR 'Blood Pressure'^{Mesh} OR 'Hypertension'^{Mesh})) AND ((vinyl dithiin) OR (thiosulfinates) OR (diallyl derivative) OR (s-allyl cysteine) OR (kyolic) OR (kwai) OR (knoblauch) OR (garlic oil) OR (garlic extract) OR (dipropyl disulfide) OR (dipropyl disuphide) OR (diallyl disulfide) OR (diallyl disulphide) OR (allyl mercaptan) OR (alliinase) OR (allicin) OR (alisat) OR (ajoene) OR (ajo) OR (allium sativum) OR (garlic) OR ('Garlic'^{Mesh}))) AND ((Humans^{Mesh}) AND (adult$^{MeSH:noexp}$ OR middle age^{MeSH} OR (middle age^{MeSH} OR aged^{MeSH}) OR aged^{MeSH} OR aged, 80 and over^{MeSH}))
EMBASE	('human-' / all SUBHEADINGS in DEM,DER,DRM,DRR) and ('blood-pressure' / all SUBHEADINGS in DEM,DER,DRM,DRR) and ('garlic-' / all SUBHEADINGS in DEM,DER,DRM,DRR)
CINAHL	('Blood-Pressure' / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) and ('Garlic-' / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE)
IBIDS	+garlic +'blood pressure'
Cochrane library	Garlic and blood pressure

Roche *et al.*[14] have reported on the quality of the blood pressure measurement in medical literature. During a preliminary data analysis, however, it became clear that no single study sufficiently fulfilled the criteria used in that study. Therefore, from the list used by Roche *et al.*, five essential criteria were formulated based on a priorisation procedure (*table 3*). The methodology section of each trial was screened for the description of blood pressure measurement by two reviewers independently. A study could score a maximum of five points if each criterion was written specifically.

Table 3. *Criteria for the judgement of the quality of the blood pressure measurement reported in the included trials (n=32)*

Quality criterion	Number of studies fulfilling criterion
Blood pressure device and accuracy mentioned (yes/no)	6
Body position reported (yes/no)	13
Measurement with arm at heart level (yes/no)	0
Rest period before measurement (yes/no; at least 5 minutes)	7
Number of readings reported (yes/no; at least 2)	9

Figure 1. *Flow diagram of the process of selecting clinical trials examining the effect of garlic ingestion on blood pressure*



Comparison with earlier systematic reviews

We hypothesised that conclusions drawn by previous authors were based on differences in inclusion and exclusion criteria due to differences in evaluating trial quality. Methodological weaknesses were identified in the two earlier meta-analyses[5,6] by examining if the trials included by these authors lacked our quality criteria. Because one previous review[4] did not use a quality assessment this review was not included in the analysis.

RESULTS

Figure 1 shows the selection process. Of the 203 trials found through the initial database search, 165 possible garlic trials were identified. The crosschecking of references and reviews revealed another 17 trials.

A total of 137 studies did not meet the inclusion criteria. Another 13 trials were excluded for various reasons mentioned in *figure 1*. The remaining 32 trials were further analysed.[15-46]

Study description

Table 4 describes the trials reporting on the effect of garlic on blood pressure. Sample size ranged from 23[24] to 862[18] subjects and trials lasted from 8[23,29,46] to 156[17] weeks. Fifteen trials had blood pressure as a primary objective[16,19-23,26,30-32,36-37,41,43,45] and 16 trials comprised of hypertensive patients.[16,18-24,26-27,31-32,34-35,41,44]

Different study designs were used; 21 double-blind, randomised, placebo-controlled, parallel trials;[15-17,20-21,25,27-28,30,32-39,42-45] two randomised placebo-controlled crossover trials;[40,41] one single-blind, placebo-controlled trial;[46] one double-blind, randomised trial against an active component;[32] six uncontrolled before-after trials;[18,22-24,26,29] one controlled before-after trial.[19] Only one trial was *a priori* set up in a randomised placebo-controlled fashion to test solely whether garlic lowers blood pressure in a hypertensive population.[16]

Some trials lacked important data. Fourteen trials did not report any numerical blood pressure data. Two studies reported no demographic data,[17,37] 14 studies[24,28-30,35,36-39,41-42,44-46] did not explicitly exclude patients on hypertensive medication and in two trials such medication was allowed.[27,33]

Table 4. *Summary of the 32 clinical trials of more than eight weeks examining the effect of garlic ingestion on blood pressure*

Author (publication year) [reference number]	Sample size	Primary objective	Blood pressure	Intervention (total daily intake in grams)	Control group (total daily intake in grams)	Co-interventions	Trial length (in weeks)
Adler et al. (1997)[15]	50	LP	N	GP (0.9)	PL	Primrose oil	12
Auer et al. (1990)[16]	47	LP + BP	H	GP (0.6)	PL	NG	12
Bordia et al. (1989)[17]	432	reinfarction	NND	GO (NND)	PL	NG	156
Brewitt et al.(1991)[18]	862	LP	H	GP (6-12)	No placebo group	NG	26
Cheng et al. (2006)[19]	79	LP +BP	H	GP (0.012) + diuretic	Diuretic	Diuretic	52
Czerny et al. (1996)[20]	100	LP + BP	H	GO (0.4) + lecithin	PL	NG	14
De A Santos et al.(1993)[21]	60	LP + BP	N + H	GP (0.9)	PL	DA	24
De A Santos et al. (1995)[22]	80	LP + BP	N + H	GP (1.8)	GO (0.006)	NG	16
Dhawan et al. (2004)[23]	40	LP + BP	N + H	Garlic pearls (0.4)	Garlic pearls (0.4)	NG	8
Durak et al. (2004)[24]	23	LP	N + H	Garlic extract (10)	No control group	NG	16
Gardner et al. (2001)[25]	53	LP	N	GP (0.3-1.0)	PL	DA	12
Grünwald et al. (1992)[26]	48	LP + BP	N + H	GP (0.6)	No placebo group	NG	18
Holzgartner et al. (1992)[27]	98	LP	N + H	GP (0.9)	Bezafibrate (0.6)	NG	12
Isaacsohn et al. (1998)[28]	50	LP	N	GP (0.9)	PL	DA	12
Jabbari et al (2005)[29]	50	LP	N	Raw garlic (1)	Raw garlic (1)	NG	8*
Jain et al. (1993)[30]	42	LP + BP	N	GP (0.9)	PL	NG	12
Kandziora (1988)[31]	40	BP	H	GP (0.6)	Diuretic-reserpin combination	Lifestyle advice	12
Kandziora (1988)[32]	40	BP	H	GP (0.6) + diuretic	PL + diuretic	Low salt diet	12
Kiesewetter et al. (1993)[33]	80	Pain-free walking distance	NND	GP (0.8)	PL	Physio-therapy	12
Lutomski (1984)[34]	102	NG	N + H	GP (0.3) + rutin	PL	NG	12
Macan et al. (2006)[35]	52	Warfarin safety	N + H	Garlic solution (0.008)	PL	NG	12
Mansell et al. (1996)[36]	60	BP	NND	GP (0.9)	PL	NG	12
McMahon et al. (1992)[37]	42	BP	NND	GP (0.9)	PL	NG	12
Mrozikiewicz et al.(1988)[38]	NND	NG	NND	GP (0.9/1.8) or GO (3)	PL	NG	12
Saradeth et al. (1994)[39]	72	LP	N	GP (0.6)	PL	NG	15
Simons et al. (1995)[40]	31	LP	N	GP (0.9)	Lactose	NG	12*
Steiner et al. (1996)[41]	52	LP + BP	N + H	GP (2.4)	PL	DA	24*
Superko et al. (2000)[42]	50	LP	N	GP (0.9)	PL	DA	12
Turner et al. (2004)[43]	75	LP + BP	N	GP (0.92)	PL	NG	12
Vorberg et al. (1990)[44]	40	NG	N + H	GP (0.9)	PL	NG	16
Zhang et al. (2000)[45]	36	BP	N	GO (0.012)	PL	NG	16
Ziaei et al. (2001)[46]	100	LP	N	GP (0.8)	PL	NG	8

BP = blood pressure; DA = dietary advice with adequate instruction; GO = garlic oil; GP = garlic powder; H = hypertensive; LP = lipids; N = normotensive; NND = no numerical data available; NG = data not given; PL = placebo. *Crossover studies; only the first parallel arm.

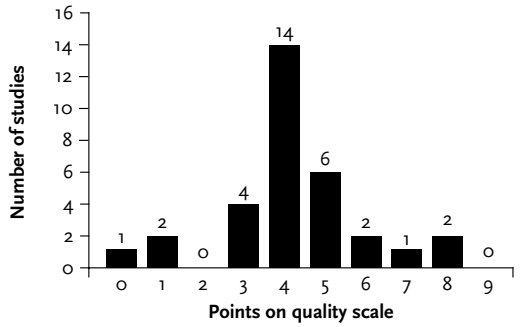
Methodological quality

Figure 2 shows how well studies performed on the methodology scale. No trials scored maximum. The median score was four points (range 0-8). Eleven trials scored five or more points.[21,25,27-28,30,33,35,40,43-45] Trials scored low for intention-to-treat analysis, allocation concealment (i.e., shielding those who admit participants to a study from knowing the upcoming assignments) and for the blinding of evaluators. This is shown in *table 2*. Randomisation[15-17,19-22,25,27-46] and providing the same treatment among treatment arms[15-17,19-23,28-46] were fairly well described in the selected studies.

Blood pressure measurement

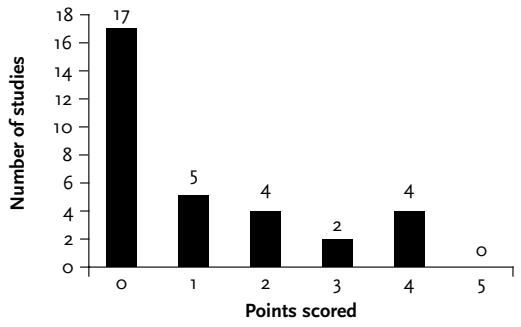
Figure 3 depicts the spread of scores on reporting the five blood pressure criteria. Scoring was poor. Half of the trials did not report any criterion[17-21,24,26-27,29,34-39,42,46] and only six trials scored three points or more.[23,25,30,40,43,45] A subdivision of the scoring system is shown in *table 3*. Information about the five criteria was scarce; no trial reported arm height during measurement and less than a quarter described the blood pressure device[25,30,40,41,43,45] or the resting period.[23,25,30,33,40,43,45] Body position was most often cited.[15,16,22-23,25,28,30-33,40,43-44]

Figure 2. *Spread of quality scores on the methodology of the selected clinical trials (n=32)*



No points indicates a high suspicion of bias. The quality criteria are mentioned in table 2.

Figure 3. *Spread of scores of the quality of blood pressure measurement as reported in the selected clinical trials (n=32)*



The 5 criteria are depicted in table 3.

Comparison with earlier meta-analysis

Of the 32 studies, 13 have been studied by either Ried *et al.*[6] or Silagy and Neil.[5] The latter also included one study lasting less than eight weeks.[47] The quality of these studies is summarised in *table 5*. All trials lack proper allocation concealment, blinding of evaluators and intention-to-treat analysis. Moreover, there was little information about the quality of blood pressure measurement. None of the trials provided information about arm height. Only two trials[30,40] mentioned resting period, the device used, body position of the patient and number of readings.

Trials with highest scores in both our quality assessments are summarised in *table 6*. For clarity cutoff points of 5 and 3 were used for the methodology score and the blood pressure score respectively. Garlic did not lower blood pressure in any selected trial. However, none of these trials were performed in hypertensive subjects.

DISCUSSION

Our main conclusion is that the hypotensive effect of garlic cannot be ascertained, because conclusions from previous meta-analyses have been based on trials with inadequate study designs, with methodological defects and with insufficient information on blood pressure measurement. Moreover, trials with the best methodology were performed in normotensive subjects.

This study shows that designs of trials on the effect of garlic on blood pressure have important flaws. Few trials used only hypertensive subjects. Only one trial was set up in a randomised, placebo-controlled, double-blind fashion to evaluate the effect of garlic on blood pressure in a hypertensive population. Although other study designs may be used, these are prone to the introduction of bias. Moreover, it may be questionable, but not entirely ruled out, that effects found in normotensive subjects can be extrapolated to hypertensive patients.

Secondly, the methodological quality was poor. No trials reported intention-to-treat analysis and only a minority had an adequate allocation concealment and blinding of evaluators. This is in agreement with two previous systematic reviews on the effect of garlic on blood pressure.[4,5] Using another methodology scale, Silagy and Neil scored for randomisation, intention-to-treat analysis and for blinding of the evaluators.[5] None of their eight included trials[16,21,27,30,31-32,44,47] scored positive on all points and they therefore concluded that 'quality assessment of the trials was generally poor'. These trials also scored weak in our rating scales (*table 5*). Another systematic review by Ackermann *et al.*[4] did not perform a systematic quality analysis. However, they do provide some overview of trial quality mainly corroborating with our findings. Ackermann *et al.*[4] refrained from carrying out a meta-analysis because 'about half of the studies did not present numerical data, multiple blood pressure measurements were used and few studies had *a priori* hypotheses related to blood pressure.'

In trials on complementary medicine in general, others have also reported low methodological quality.[7,48] Linde *et al.*[7] reviewed trials on homeopathy, acupuncture and herbal medicine, garlic not included. They concluded that most trials had inadequate allocation concealment, poor randomisation procedures and gave little information about dropouts. In a more comprehensive review, Gagnier *et al.*[48] analysed 1321 English trials on herbal medicine, garlic included. They concluded that trials in herbal medicine provided less than half of the necessary information in their reports. Of the ten herbs studied, garlic trials scored second worst. Allocation concealment, randomisation and

Table 5. *Quality analysis of the 14 included trials in the meta-analyses performed by Ried et al.[6] or by Silagy and Neil[5]*

Author (year) [reference]	Included by Ried (R) or Silagy (S)	Total points quality scale (max. 9)	Lacking items	Total points blood pressure scale (max. 5)	Lacking items
Adler (1997)[15]	R	4	AC, PB, EB, CG, IT	1	DM, AH, RP, NR
Auer (1990)[16]	R + S	4	AC, EB, CG, D, IT	1	DM, AH, RP, NR
De A Santos (1993)[21]	S	6	AC, EB, IT	0	DM, AH, BP, RP, NR,
Holzgartner (1992)[27]	R + S	5	AC, EB, IT, ST	0	DM, AH, BP, RP, NR
Jain (1993)[30]	R + S	5	AC, EB, D, IT	4	AH
Kandziora (1988)[31]	S	4	AC, PB, EB, D, ITT	2	DM, AH, RP
Kandziora (1988)[32]	R + S	4	AC, EB, D, IT	2	DM, AH, RP
Kiesewetter* (1991) [47]	S	4	AC, EB, CG, D, IT	0	DM, AH, BP, RP, NR
Kiesewetter (1993)[33]	R	5	AC, EB, D, IT	2	DM, AH, NR
Saradeth (1994)[39]	R	4	AC, EB, CG, D, IT	0	DM, AH, BP, RP, NR
Simons (1995)[40]	R	5	AC, EB, CG, IT	4	AH
Steiner (1996)[41]	R	4	AC, EB, CG, D, IT	1	BP, AH, RP, NR
Vorberg (1990)[44]	R + S	5	AC, EB, CG, IT	1	DM, AH, RP, NR
Zhang (2000)[45]	R	6	AC, EB, D, IT	3	BP, AH

AC = allocation concealment; PB = patient blinding; EB = evaluators blinding; D = dropouts; CG = comparable groups; IT = intention-to-treat analysis; ST = same treatment of groups; DM = device mentioned; AH = arm at heart level; BP = body position; RP = resting period; NR = number of reading. *Not included in our systematic review because of a treatment period of less than eight weeks.

Table 6. *Summary of the five clinical trials on the effect of garlic on blood pressure with the highest methodological quality score and highest score for the quality in reporting blood pressure measurements*

Author (year) [reference]	Blood pressure a primary goal	Hypertensive population	Methodological quality*	Blood pressure quality**	Garlic effective in lowering blood pressure
Gardner (2001)[25]	No	No	7	4	No
Jain (1993)[30]	No	No	5	4	No
Simons (1995)[40]	No	No	5	4	No
Turner (2004)[43]	Yes	No	8	4	No
Zhang (2000)[45]	Yes	No	6	3	No

***Score based on the criteria proposed by the Dutch Cochrane society. No points indicates a high suspicion of bias. A cutoff value of five points or more was chosen. **Blood pressure quality was scored on reporting on exact device, body position, arm at heart level, resting period and number of readings reported. A maximum of five point could be obtained. A cutoff value of three points was chosen.**

blinding of the evaluators, as in the present study, were poorly described.

Our conclusion on the methodological quality contrasts with the work by Ried *et al.*[6] however. In their systematic review they also used guidelines by the Cochrane Collaboration for assessing trial quality. They concluded on the basis of their analysis that trial quality of their included trials was 'generally high'. However, they only provided information about blinding, randomisation and blood pressure as a primary outcome. Our analysis shows that what trials mostly lack is an adequate allocation concealment, blinding of the evaluators and proper use of an intention-to-treat analysis. It has been shown that inadequate allocation concealment or blinding may lead to exaggerated treatment effects.[10,50,51] When taking into account all nine quality criteria, the performance of the included garlic trials is, at least, equivocal.

The third conclusion that can be drawn from our results is that trials provide insufficient information about the technique used to measure blood pressure. The absence of proper information about blood pressure measurements is worrying since factors such as arm position may influence blood pressure measurements by up to 10 mmHg.[12] The fact that only 15 studies had blood pressure as a primary outcome might explain this absence. One could argue it is not the blood pressure per se that counts but rather the difference between the measurements. However, incorrect

blood pressure measurements would inherently lead to data pollution of normotensive and hypertensive subjects making conclusions impossible. Besides, none of the studies included in the present review described that blood pressure was measured similarly every time.

To our knowledge, the present study is the first review that systematically assessed blood pressure measurement in garlic trials. Of the three previous systematic reviews on garlic and blood pressure, only Ried *et al.*[6] provide data about blood pressure measurements, but they do not draw the conclusion that the information was insufficient. Roche *et al.*[14] have reviewed the reporting of blood pressure measurements in leading English medical journals. In their analysis of 116 papers, device accuracy and validation or reporting of arm level was also poorly described; device accuracy was only reported in 3% and arm level in 5%. As in the present study, both body position and number of readings were best reported. Also in a review of Brazilian medical literature, Holanda *et al.*[49] showed articles lacked important data; in only half of the studies the type of sphygmomanometer or the number of readings were mentioned and only a quarter described the body position.

Did the inclusion of these garlic trials affect the conclusions of previous meta-analyses? In our view the absence of a proper methodology may have indeed affected outcome. Both Schulz *et al.* and Moher *et al.* have shown that inadequate allocation concealment and lack of blinding may lead to exaggerated results.[50,51] In the present study it was shown that garlic trials scored poorly in both criteria. Biased results in trials may also affect results of systematic reviews.[10] According to the criteria put forward in the present study, only five trials provide sufficient quality data (*table 6*).[25,30,40,43,45] These studies do not show an effect of garlic on blood pressure. We refrained from conducting a meta-analysis, however, because all trials were performed on normotensive subjects. In our view these trials are not suitable to answer the only clinically relevant question whether garlic lowers blood pressure in hypertensive patients.

Our analysis has several limitations. Our scoring systems inherently had some subjective elements. We minimised this effect by using two independent evaluators and a standardised checklist. Second, the absence of reporting procedures in the garlic trials does not necessarily imply these procedures were not done. Our criteria might have been biased towards precisely written studies. It is our opinion, though, that transparency is a key element in conducting trials. In such a way, clear writing might in itself be a quality criterion. Deficient reporting generally embodies imperfect methodologies.[10] Thirdly, the applicability of scores to appraise the methodological quality has been challenged by others,[8,10] arguing that high scores do not necessarily represent valid trials. They propose that relevant methodological aspects should be assessed individually.[10] We therefore used both, because in our view an overall composite score nevertheless gives a pragmatic and visual tool for a global quality assessment.

CONCLUSION

It is our view that garlic cannot be recommended to lower blood pressure in the daily practice of physicians working in the field of hypertension treatment, given the low methodological quality, the lack of information about blood pressure measurement and the absence of methodological sound trials in hypertensive patients.

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ORIGINAL ARTICLE

Impact of anthracycline dose on quality of life and rehabilitation in breast cancer treatment

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ABSTRACT

Background: In 2005 the Dutch national guidelines for treatment of breast cancer were updated. From then onwards, patients with operable breast cancer, who formerly received four cycles of adjuvant chemotherapy with doxorubicin/cyclophosphamide (AC), were treated with five cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC), based on data suggesting survival benefit.

Primary objective: evaluation of the effect on quality-of-life and trainability after four AC versus five FEC cycles of polychemotherapy. Secondary objective: evaluation of the effectiveness of an 18-week training programme for breast cancer survivors.

Methods: A prospective cohort study design was used, comparing two chemotherapy regimens historically. The first cohort (group 1) received 4AC (A 60 mg/m², C 600 mg/m²) (n=25) and the second cohort (group 2) received 5FEC (F 500 mg/m², E 90 mg/m², C 500 mg/m²) (n=50) adjuvant polychemotherapy. Both groups completed an 18-week high-intensity strength-training programme. Outcome measures were changes in quality-of-life (EORTC-QLQ-C30, MFI-20), muscular strength (one-repetition maximum; leg press) and cardiopulmonary function (VO2max) between baseline and follow-up.

Results: Between March 2002 and February 2006, 75 female subjects with breast cancer participated in this study. Baseline characteristics were similar in both groups. After completing the training programme, both groups showed a significant improvement in all outcome measures. No significant differences in changes of the EORTC-QLQ-C30 and MFI-20, one repetition maximum of the leg press and the VO2max between the two groups were demonstrated.

Conclusion: After adaptation of the Dutch national breast cancer treatment guidelines, patients received prolonged and increased doses of anthracyclines. This, however, did not result in a difference in the baseline situation before rehabilitation and in training response, nor in quality of life between the two groups.

KEYWORDS

Anthracycline treatment, operable breast cancer, quality of life

INTRODUCTION

More women survive breast cancer than any other type of cancer, partly owing to the improved treatment possibilities. Therefore, the need to learn more about the effect of adjuvant chemotherapy on (long-term) quality of life (QoL) is growing. Breast cancer patients, who are subjected to adjuvant chemotherapy, suffer from emotional and physical side effects. Fatigue and loss of physical performance are the most frequently reported symptoms by (breast) cancer patients. This is mainly caused by an impaired cardiopulmonary function and diminished muscular strength.[1] Many of these patients perceive fatigue as the most distressing symptom associated with their illness because it imposes limitations on their physical activity level.[2]

Other side effects are nausea, pain, changes in body composition, changes in mood state and sleep difficulties.[1]

In 2005 the Dutch national guidelines for treatment of breast cancer were updated. From then onwards, patients with operable breast cancer, who formerly received four cycles of adjuvant chemotherapy with doxorubicin/

cyclophosphamide (AC), were treated with five cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC), based on data suggesting survival benefit.[3] However, no data are available on the extent to which prolonged and increased doses of anthracyclines effect QoL and rehabilitation post-chemotherapy.

The use of anthracyclines is limited by dose-dependent cardiotoxicity.[4] The threshold anthracycline level was not exceeded in either group, so it is unlikely that an additional anthracycline cycle might result in a more prominent decline in cardiopulmonary function. But it has not been ruled out that a prolonged and increased dose of anthracyclines and in addition 5-fluorouracil might cause cumulative side effects, which can impair QoL and trainability. Several studies have consistently demonstrated that physical exercise has a positive effect on QoL following cancer diagnosis, including physical and psychological well being, and may thereby be an effective tool to reverse several side effects of cancer treatment with chemotherapy.[1,2,5,6] Therefore, not only the difference in side effects, but also the adaptive response to a training programme is relevant when comparing treatment regimes. To evaluate this training response a high-intensity physical-strength training programme was initiated.

AIM

The primary objective of this study was to determine the influence of prolonged and increased anthracycline doses and addition of 5FU (5FEC *vs* 4AC), as determined by adapted guidelines, on QoL and trainability.

A secondary objective was to evaluate the effectiveness of an 18-week training programme on QoL and trainability in breast cancer survivors.

PATIENTS AND METHODS

This study is a subanalysis from a large running study examining the value of an 18-week training programme.[6] We used a prospective cohort study design, comparing two chemotherapy regimens historically, with a pre- and post-test design, in the Maxima Medical Centre (MMC) teaching hospital in Veldhoven and Eindhoven. This project was performed by the Department of Internal Medicine and Sports Medicine. The project was approved by the Ethics Review Committee of the MMC and informed consent was obtained from all patients. Based on the current national guidelines at the time, the first cohort (group 1) received 4AC (A 60 mg/m^2, C 600 mg/m^2) and after adaptation of the national guidelines the second cohort (group 2) received 5FEC (F 500 mg/m^2, E 90 mg/m^2, C 500 mg/m^2) adjuvant polychemotherapy.

Both groups completed an 18-week high-intensity physical-strength training programme.[6,7] Tests were performed at week 0 and week 18. Eligibility criteria included histologically confirmed breast cancer with no indication of recurrent or progressive disease, age between 25 and 70 years, completion of surgical treatment, adjuvant chemotherapy and radiotherapy 6 to 52 weeks before starting the training programme. We excluded subjects who suffered from serious diseases (cardiac failure, COPD, neurological disorders), which limited their physical performance capacity. Outcome measures were changes in QoL (EORTC-QLQ-C30, MFI-20), muscular strength (one-repetition maximum; leg press) and cardiopulmonary function (VO2max) between baseline and follow-up.

Measurements

Patient characteristics at baseline were documented. Height and weight were measured. Additionally simple measures for body composition were performed and the body mass index (BMI) was calculated. Skin folds at biceps, triceps, subscapular and suprailiac were measured and percentage body fat was determined from body weight and the skin fold measurements using the equation of Durnin and Womersley.[8]

One-repetition maximum (1RM) of the leg press is a test to determine muscular strength.[9] 1-RM is the maximum amount of weight that can be lifted once. Indirect 1RM values were calculated from the Brzycki equation.[10] 1RM is stated in kilograms in proportion to body weight. The weight a subject was training with during the programme was used for the test, in addition to which the physiotherapist estimated a weight that could be performed at best ten times. This test was performed at the start (week 0) and at the end of the programme (week 18).

A VO2max test was performed to define the individual aerobic capacity and is a test to determine cardiopulmonary function. The test was performed on a cycle ergometer with a ramp protocol[11] under supervision of a sports physician. An oxymeter was used to obtain breath samples and to analyse O2 and CO2 concentrations. Patients were instructed to cycle with a pedal frequency of 70 to 80 revolutions/min and encouraged to continue exercise until exhaustion. The test was ended if patients were unable to maintain the required pedalling frequency and when the patient indicated that he/she could not go any further. This test was performed at the start (week 0) and at the end of the programme (week 18).

To determine the effects of the exercise training programme on QoL and on fatigue, two questionnaires were used as effect parameters. Both questionnaires were completed in week 0 and week 18.

The EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire version 2) is a self-reporting QoL questionnaire developed

for use in clinical trials in oncology.[12] It consists of five functional scales regarding physical, role, emotional, cognitive and social function. Secondly it consists of a scale of global health status and QoL. Thirdly a scale regarding symptoms (subdivided into fatigue, emesis and pain). And lastly, the questionnaire contains questions concerning six single items: dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact. The MFI questionnaire (Multidimensional Fatigue Inventory) was especially developed to examine fatigue in cancer patients and includes the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation.[13]

Training programme

The 18-week training programme consisted of high-intensity resistance and interval training. To counteract bias resulting from spontaneous recovery after chemotherapy, training started no earlier than six weeks after completing chemotherapy. The patients trained in groups of six to eight persons on specialised resistance training equipment and on bicycle ergometers under the supervision of physical therapists. During the first 12 weeks, patients trained twice a week. The last six weeks, patients trained once a week.[6,7]

During the training programme patients could participate in a psychological programme, which was followed once a week for a seven-week period.

Statistical analyses

Statistical analyses were performed using the SPSS version 13.0. Patients in both groups were analysed for differences in age, height, weight, fat percentage, BMI and time from last treatment of chemotherapy, using independent samples *t*-tests. Differences between both groups in number of lymph nodes and receiving radiotherapy or not was analysed using the χ^2 tests. Differences in mean scores for VO2max, 1RM leg press, EORTC-QOL-C30 and MFI between both groups were analysed using independent samples *t*-tests. Paired sample t-tests were used to test the significance of changes in the mean scores from baseline (week 0) to post-intervention (week 18). A p value <0.05 was used to indicate statistical significance.

The factors number of lymph nodes, addition of radiotherapy and the time between last received chemotherapy and start of the training programme were considered to influence physical capacity. These items were included as covariates in an ANCOVA analysis, but their influence did not seem to change the outcome.

Because of the great inter-patient differences, it was not possible to extrapolate and fill in the missing values. Therefore, the subjects with one or more missing value were left out of the analysis.

RESULTS

Between March 2002 and February 2006, 75 female subjects with breast cancer participated in this study. The first cohort consisted of 25 subjects, treated in the period of March 2002 to January 2005. The second cohort comprised 50 subjects treated in the period of January 2005 to February 2006.

Although the study design did not allow randomisation, baseline characteristics were similar in both groups as illustrated in *table 1*. The factors number of lymph nodes, addition of radiotherapy and the time between last received chemotherapy and start of the training programme were tested as covariates, but their influence did not seem to change the outcome.

After completing the 18-week training programme, both the AC and FEC group showed a significant improvement in muscular strength (one-repetition maximum; leg press) and cardiopulmonary function (VO2max) between baseline and follow-up (*table 2*). Both groups also showed improvement in QoL (EORTC-QLQ-C30, MFI-20) (*figures 1A, 1B* and *2*).

Concerning the EORTC-QLQ-C30, the AC and FEC group showed significant improvements in physical functioning (AC: p=0.015, FEC: p<0.0001), role functioning (AC: p=0.003, FEC: p=0.01), social functioning (AC: p=0.003, FEC: p=0.001) and global health status (AC: p=0.01, FEC: p=0.001). Furthermore, a reduction in fatigue (AC: p=0.025, FEC: p<0.0001) was found in both groups and in dyspnoea only in the FEC group (p=0.004). All other items, except diarrhoea (AC), cognitive functioning and constipation (FEC), improved, although not significantly (p>0.05). Concerning the MFI-20, significant reductions in both groups were found for general fatigue (AC: p=0.05,

Table 1. *Patients characteristics*

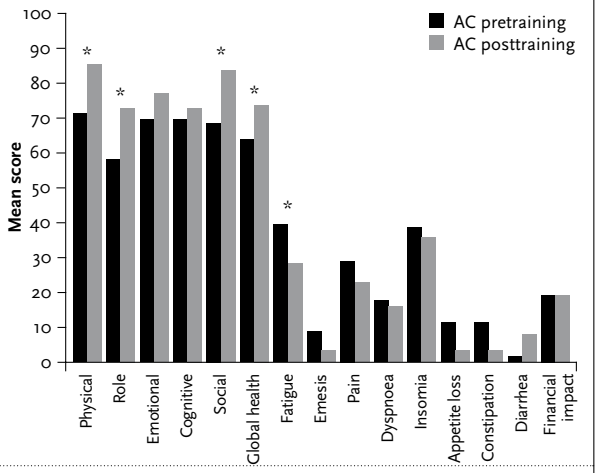
	AC (n=25) Mean (± SD)	FEC (n=50) Mean (± SD)	p-value
Age (years)	49.0 (7.8)	49.7 (8.3)	0.8
Height (cm)	166.3 (6.4)	168.2 (6.0)	0.2
Weight (kg)	73.2 (17.5)	72.8 (14.4)	0.9
Fat (%)	36.5 (5.6)	37.2 (4.8)	0.6
BMI (kg/m^2)	26.4 (5.7)	25.7 (4.9)	0.6
Time between chemo-therapy and training (weeks)	23.3 (12.8)	17.1 (8.5)	0.4
Lymph nodes:			0.07
• 0	12	14	
• ≥1	12	35	
• Unknown	1	1	
Radiotherapy:			0.9
• Yes	18	37	
• No	7	13	

Table 2. *VO2max and IRM leg press training results AC versus FEC*

	VO2max				1RM leg press			
	Pre-training (ml/min)	Post-training (ml/min)	Change* (%)		Pre-training (kg/kg bodyweight)	Post-training (kg/kg bodyweight)	Change* (%)	
	Mean (± SD)	Mean (± SD)	Mean (± SD)	p-value**	Mean (± SD)	Mean (± SD)	Mean (± SD)	p-value**
AC (VO2max n=22/ IRM leg press n=23)	1782 (417)	2060 (412)	12.3 (10.6)	<0.0001	122.8 (35.3)	161.5 (43.0)	56.0 (47.2)	<0.0001
FEC (VO2max n=43/ IRM leg press n=43)	1774 (271)	1991 (352)	13.3 (14.8)	<0.0001	136.8 (34.0)	164.3 (40.4)	46.6 (26.2)	<0.0001
P value#	0.9	0.5	0.8		0.1	0.8	0.4	

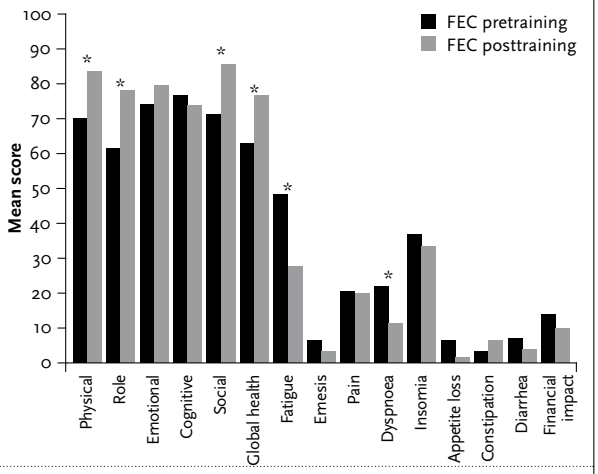
*The percentage progression made after completing the training programme. **The p values on the vertical row refer to the significance of the trainings effect: post- *vs* pre-training. #The p values on the horizontal row refer to the significance of the trainings results compared between the two groups: AC *vs* FEC.

Figure 1A. *Mean scores of the EORTC-QoL-C30 AC group*



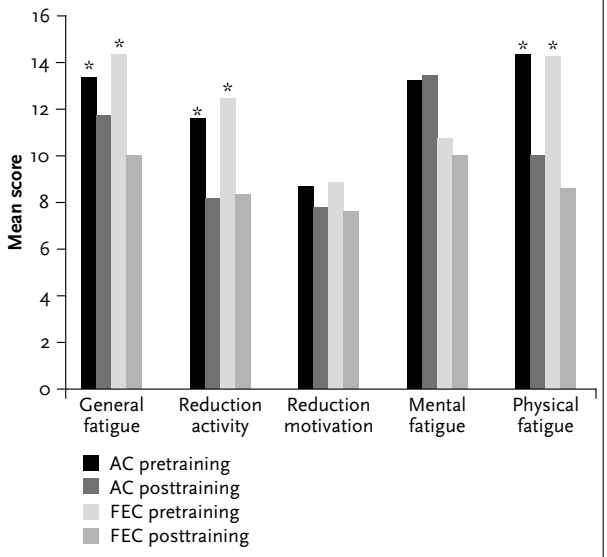
In black the pre-training results are shown and in grey the post-training results. *Values that are significant.

Figure 1B. *Mean scores of the EORTC-QoL-C30 FEC group*



In black the pre-training results are shown and in grey the post-training results. *Values that are significant.

Figure 2. *Mean scores of the MFI*



In black the pre-training results of the AC group are shown and in dark grey the post-training results. In white the pre-training results of the FEC group are shown and in light grey the post-training results. *Values that are significant.

FEC: p<0.0001), reduction of activity (AC: p=0.003, FEC: p<0.0001) and physical fatigue (AC: p<0.0001, FEC: p<0.0001). The subscale reduction of motivation improved for both groups but not significantly (p>0.05), as well as the subscale mental fatigue for the FEC group. The subscale mental fatigue did not improve post-training in the AC group.

When the training response of the two groups was compared, no significant differences in changes of the one repetition maximum of the leg press and the VO2max were found (*table 2*); no significant differences in changes of the EORTC-QLQ-C30 and MFI-20 between the two groups were demonstrated either.

DISCUSSION

After adaptation of the national breast cancer treatment guidelines, patients received prolonged and increased doses of anthracyclines. To our knowledge, no studies have been carried out comparing the effect of 4AC *vs* 5FEC on trainability and QoL. It could be anticipated that addition of an extra anthracycline cycle (5FEC) and the addition of 5-fluorouracil might result in more cumulative side effects, hence worsening the outcome measurements. We did not, however, observe any differences in training response or in quality of life between the two compared groups. Therefore we conclude that the adaptation of the national guidelines for treatment of breast cancer based on improved survival, does not significantly alter the trainability of the patient.

This is a non-randomised study in which the choice of a specific chemotherapeutic regime was determined by the adaptation of the national breast cancer guideline. For this reason no power analysis in advance was possible; for the number of patients enrolled in our study, we were dependent on the time-related choice of a therapeutic regimen. The second cohort is double the size of the first cohort. This is explained by the fact that accrual in the beginning of the study went slowly and patients were still being treated with an alternative regimen chemotherapy (CMF), so they could not participate in our study. During the second phase of our study two hospitals merged and patients from two locations could participate. This resulted in a faster accrual. Although the numbers are not the same in both groups, the patient characteristics are. In our opinion comparison between the two groups in this way is very well possible. It cannot be ruled out that in a double-blind randomised study with a higher number of patients, a statistical significant difference in trainability and QoL between the two groups might have been found.

We did not encounter medical problems during the training programme. Seventy-five patients started and completed the programme. Because of logistic reasons some patients missed one of the testing dates. These patients were left out of the analysis. The exact number of patients used in the analysis is listed in *table 2*.

From a previous pilot study and a long-term follow-up study by Backer *et al.*,[6,7] it appeared that the cancer rehabilitation programme of the MMC consisting of a combined muscular strength and endurance programme to improve physical capacity in cancer patients shows positive results. Several other studies have reported the effect of an exercise programme after chemotherapy for breast cancer patients, although other outcome measures were used.[1,14,15] The positive results demonstrated in the studies are improvements on top of spontaneous improvement in the time after chemotherapy. Our study confirms the effect of a training programme in breast cancer patients on physical condition. Although we did not use a control group who did not follow the training programme, we found significant improvement of trainability and QoL in both patient groups before and after completing the training programme.

QoL is a more difficult parameter, but at the same time the most valuable for the cancer patient. We assume that improvement of muscular strength and cardiopulmonary function in patients will lead to a better performance of daily activities and resumption of their jobs. This has great impact on economic status and social functioning. Schou *et al.* show in their study that women with breast cancer scored significantly lower on emotional, cognitive, and social functioning at time of diagnosis compared with the general female population, and continued to score lower on cognitive and social functioning one year after surgery. Chemotherapy was predictive for poorer role functioning one year after surgery.[16] Earlier studies confirm the positive effect of (weight) training programmes on QoL in breast cancer survivors.[17] Our study confirms the positive effect of a high-intensity physical-strength training programme on QoL.

QoL and fatigue are not only influenced by physical training. Both are multidimensionally defined. In our study the emphasis lies on physical training. Patients were able to participate in a psychological programme. But only a minority made use of this possibility and the percentage of participation in both groups was equal (20% in the AC *vs* 22% in the FEC group). Nevertheless, results could be positively influenced by participation in this programme. This can be a point of attention in future studies. Future recommendations would also be to outweigh the potential improvement of outcome in terms of survival and QoL during and after chemotherapy in any new adjuvant regime in breast cancer, such as the recent changes in the national breast cancer treatment guidelines of 2008, in which even a higher dose of anthracyclines is advised. As the number of cancer survivors increases, emphasis has to be on long-term effects of QoL as well.

CONCLUSION

After adaptation of the Dutch national breast cancer treatment guidelines in 2005, patients received prolonged and increased doses of anthracyclines. This, however, did not result in a difference in the baseline situation before rehabilitation and in training response nor in quality of life between the two groups. This preliminary survey suggests that this guideline adaptation, based on improved survival, does not substantially alter the trainability of the patient. But further study is required. This study also confirms the importance of post-chemotherapy training as shown by increase in physical exercise capacity with concomitant increases in QoL experienced by the patients.

NOTE

These data were presented as a poster presentation at the European Cancer Congress (ECCO 14) in Barcelona 23-27 September 2007, abstract: 1137. European Journal of Cancer Supplements, Vol. 5 No 4, Page 153.

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ORIGINAL ARTICLE

Hip surgery sequentially induces stress hyperglycaemia and activates coagulation

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ABSTRACT

Background: A frequent complication of orthopaedic procedures is venous thromboembolism (VTE). Hyperglycaemia has been shown to activate the coagulation system and is associated with postoperative morbidity and mortality. Therefore, we hypothesised that glucose levels increase during orthopaedic surgery and are associated with an activation of the coagulation system.

Methods: Nine adult patients undergoing elective hip replacement were included. Venous blood samples were taken before, during and after surgery. Plasma glucose levels, factor VIII clotting activity (fVIII:c), von Willebrand ristocetin cofactor activity, von Willebrand factor antigen and prothrombin fragment 1+2 were measured.

Results: Immediately after induction of anaesthesia, plasma glucose levels started to increase until the second day postoperatively (peak 8.0 mmol/l). After seven weeks glucose values had returned to baseline (6.1 mmol/l), $p<0.001$ with ANOVA. All coagulation parameters increased during surgery, subsequent to the rise in glucose. The change in mean FVIII:c and von Willebrand ristocetin cofactor activity was significantly correlated with mean glucose values.

Conclusions: These observations indicate that total hip replacement surgery causes an increase in glucose levels that precedes the proportional rise of the measured coagulation parameters. This suggests a possible role of glucose in the activation of the coagulation system during hip surgery.

KEYWORDS

Coagulation activation, orthopaedic surgery, stress hyperglycaemia

INTRODUCTION

A frequent complication of surgical procedures is venous thromboembolism (VTE), manifesting as deep venous thrombosis or pulmonary embolism.[1] Especially after orthopaedic surgery the incidence of postoperative symptomatic VTE is high, occurring in 1.5 to 10% of the patients despite adequate anticoagulant prophylaxis.[2] Risk factors for the development of VTE after surgery include underlying malignancy and advanced age.[2] In an experimental setting, hyperglycaemia has been shown to activate the coagulation system in healthy volunteers, in particular by stimulating the tissue factor pathway.[3,4] This is of interest since hyperglycaemia in response to surgery is a common finding.[5-7] Counter-regulatory hormone action initiated by the surgical trauma can induce 'stress hyperglycaemia', even without known diabetes mellitus.[8] Recently, preoperative hyperglycaemia has been identified as a risk factor for pulmonary embolism, independent of diabetes mellitus.[9]

Thus, we hypothesised that glucose levels increase during orthopaedic surgery and may contribute and therefore be related to an activation of the coagulation system.

MATERIALS AND METHODS

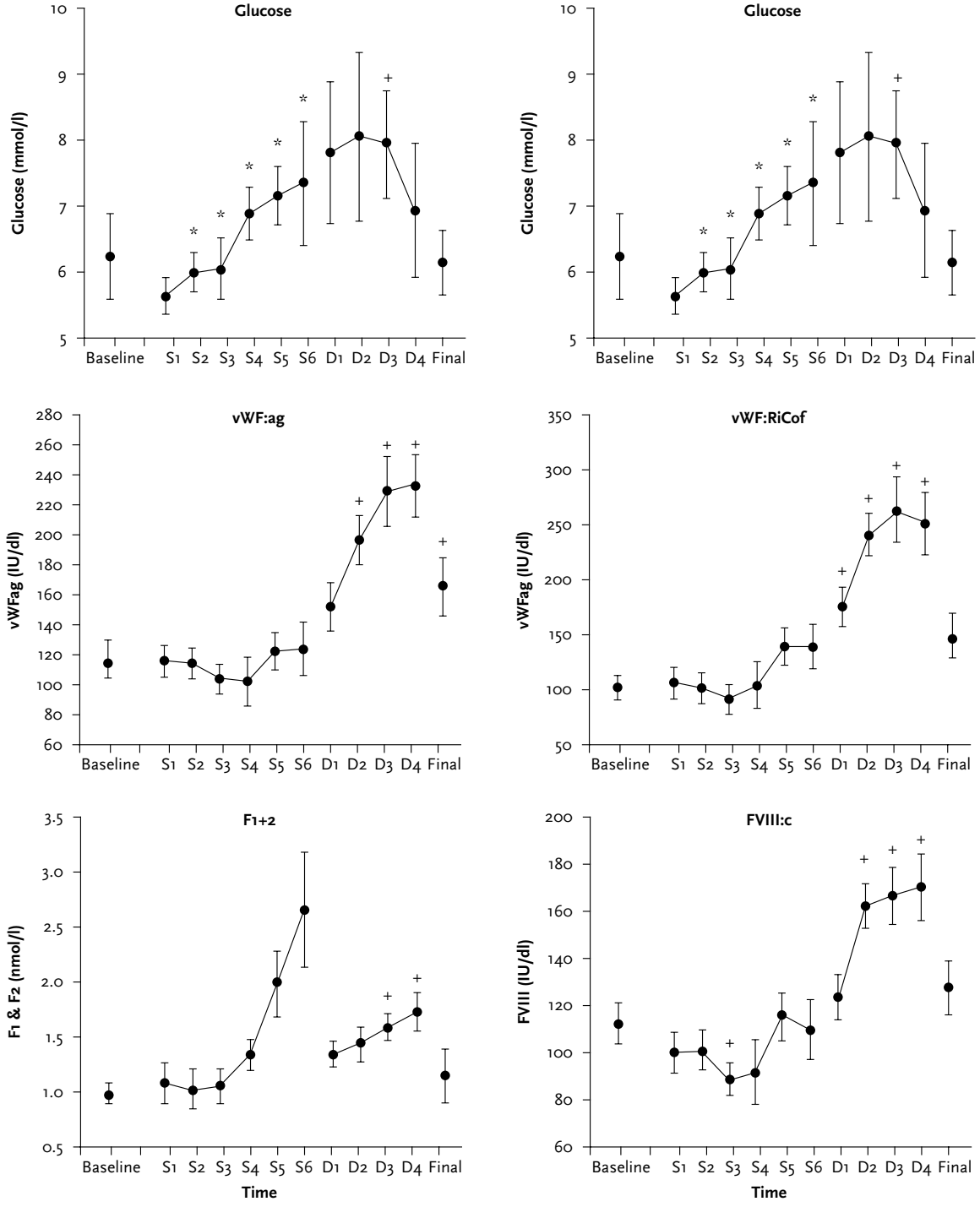
Study design and population

We performed an observational study, assessing the correlation between perioperative changes in plasma glucose levels and a number of coagulation parameters. Adult patients undergoing elective hip replacement surgery were recruited from the Department of Orthopaedic Surgery at the Academic Medical Centre, University of Amsterdam, the Netherlands. Exclusion criteria were: previous VTE, revision hip replacement, use of β-blockers, known diabetes mellitus, inability or unwillingness to give written informed consent, and inability to be followed up. The study was approved by the Medical Ethics Commission of the Academic Medical Centre, University of Amsterdam and written informed consent was obtained from each patient.

Data collection

Clinical data including date of birth, sex, height, weight, blood and indication for hip replacement were recorded. Venous blood samples were taken at 14 set points in time (*figure 1*).

Figure 1. *Mean perioperative and postoperative glucose levels (2 upper graphs are identical) and coagulation parameters with 95% CI + p<0.05 as compared with baseline, *p<0.05 as compared with S1 (glucose fasting samples only)*



Sampling time points

Baseline (n=9)	**Baseline: surgery - 1 day**	S6 (n=8)	2 hours after surgery
S1 (n=7)	Before induction	D1 (n=9)	Surgery + 1 day
S2 (n=8)	After induction	D2 (n=7)	Surgery + 2 days
S3 (n=8)	After skin incision	D3 (n=9)	Surgery + 3 days
S4 (n=8)	After placing cup	D4 (n=7)	Surgery + 4 days
S5 (n=8)	After placing prosthesis	Final (n=9)	Surgery + 49 days

Repeated measurements ANOVA: p<0.001 for glucose, vWF:ag, vWF:RiCof, F1+2 and FVIII:c.

The samples on the day of surgery were taken in the fasting state. The samples on the other days (non-fasting) were taken between 8 and 10 am to exclude the influence of circadian fluctuations on the haemostatic parameters.

Laboratory determinations

Blood was collected in ice-cooled tubes of 2.7 ml containing 0.109 M trisodium citrate, which were centrifuged within one hour. The citrate samples were centrifuged at 3000 rpm at 4°C for 20 minutes and the separated plasma again at 4000 rpm and 4°C for five minutes and stored immediately at -80°C. Plasma glucose was measured using the HK/G-6PD method (Roche/Hitachi, Basel, Switzerland) and corrected for the 10% dilution with sodium citrate. Factor VIII clotting activity (FVIII:c) and von Willebrand ristocetin cofactor activity (vWF:RiCof) assays were performed on an automated coagulation analyser (Behring Coagulation System) with reagents and protocols from the manufacturer (Dade Behring, Marburg, Germany), and are expressed as a percentage of reference activity. Measurements of prothrombin fragment 1+2 (F1+2) (Dade Behring, Marburg, Germany) and von Willebrand factor antigen (vWF:Ag) (antibodies from Dako, Glostrup, Denmark) were performed by ELISA.

Statistical analyses

Mean glucose levels perioperatively and during surgery were plotted against time. Sequential glucose values were analysed with the repeated measurements ANOVA. For the ANOVA analyses, missing values per patient were linearly interpolated. Post-hoc testing was performed using the paired t-test with Holm's sequential Bonferroni correction, comparing the non-fasting samples with the baseline mean glucose values and the fasting samples with the pre-induction sample. To assess the correlation between mean glucose levels and mean FVIII:c, vWF:Ag, vWB:RiCof, F1+2 values we calculated the correlation coefficient. Correlation was considered relevant in case of $r > 0.5$. The level of significance was $p<0.05$.

RESULTS

During the study period 17 patients scheduled for elective hip replacement surgery were evaluated. Nine patients met the inclusion criteria and provided written informed consent. The investigated cohort included five males and four females with a mean age of 63 years (SD 22 years) and mean BMI of 27.7 kg/m^2 (SD 2.8). Indication for hip surgery was coxarthrosis in seven patients, one case of idiopathic femur head necrosis and prednisone-induced femur head necrosis in one patient. This last subject had stopped taking prednisone two years before inclusion in this study. Low-molecular-weight heparin (LMWH), starting the day before surgery, was used as thromboprophylaxis in five patients. One patient started LMWH the day after surgery and three patients used oral anticoagulants.

Glucose values

Mean plasma glucose levels and the number of successful samples per time point are depicted in *figure 1* and *table 1*. The repeated measurements ANOVA for all sequential glucose samples was $p<0.001$. Missing values are due to occlusion of the intravenous sampling catheter during surgery. Mean plasma glucose levels changed significantly during surgery as compared with pre-induction. Directly after induction of anaesthesia glucose levels increased from 5.6 to 6.0 mmol/l ($p=0.002$). Two hours after surgery, glucose levels were still significantly increased as compared with pre-induction (7.3 mmol/l, $p=0.01$). Postoperatively non-fasting glucose levels peaked at the second postoperative day and remained increased up to the 4th day after surgery as compared with baseline non-fasting mean glucose values. After seven weeks, non-fasting glucose levels returned to baseline values.

Coagulation factors

The mean levels of FVIII:c, vWF:Ag, vWF:RiCof and F1+2 are presented in *table 1*. All values increased significantly during surgery. FVIII:c and F1+2 returned to baseline

Table 1. *Mean levels of glucose and coagulation parameters per time point, displayed with mean ± SD*

Time		Glucose (mmol/l)	F1+2 (nmol/l)	vWF:Ag (IU/dl)	vWB:RiCof (IU/dl)	FVIII:c (IU/dl)
Surgery - 1 day	Baseline	6.2 (±1.0)	1.0 (±0.3)	116.8 (±37.2)	101.8 (±34.3)	113.1 (±25.3)
Before induction	S1	5.6 (±0.4)	1.1 (±0.5)	115.4 (±27.5)	105.4 (±36.7)	100.9 (±23.7)
After induction	S2	6.0(±0.4)	1.0 (±0.5)	114.0 (±29.0)	101.0 (±35.2)	101.0 (±24.8)
After skin incision	S3	6.0 (±0.7)	1.0 (±0.4)	103.6 (±28.2)	91.1 (±39.6)	89.3 (±19.0)
After placing cup	S4	6.9 (±0.6)	1.3 (±0.4)	102.1 (±46.2)	104.5 (±59.8)	92.5 (±38.4)
After placing prosthesis	S5	7.2 (±0.6)	2.0 (±0.8)	122.0 (±34.8)	140.4 (±47.4)	116.3 (±28.8)
2 hours after surgery	S6	7.3 (±1.4)	2.6 (±1.5)	123.6 (±50.0)	138.6 (±58.6)	110.4 (±36.6)
Surgery + 1 day	D1	7.8 (±1.7)	1.3 (±0.4)	151.4 (±48.4)	175.9 (±54.6)	124.3 (±28.7)
Surgery + 2 days	D2	8.0 (±1.7)	1.4 (±0.4)	195.4 (±42.8)	240.6 (±52.1)	163.3 (±24.5)
Surgery + 3 days	D3	7.9 (±1.2)	1.6 (±0.4)	228.0 (±69.3)	264.0 (±87.8)	167.7 (±37.0)
Surgery + 4 days	D4	6.9 (±1.4)	1.7 (±0.5)	231.4 (±54.7)	250.6 (±71.2)	171.3 (±37.0)
Surgery + 49 days	Final	6.1 (±0.8)	1.1 (±0.7)	164.6 (±57.9)	149.2 (±62.7)	128.4 (±35.2)

values seven weeks after surgery. However, vWF:Ag and vWF:RiCof remained elevated. In *figure 1* the increase in mean levels of coagulation factors per time point are shown. In contrast with the steep increase in glucose levels after placement of the prosthesis cup (S4), vWF:Ag, vWF:RiCof and FVIII:c levels somewhat lagged behind the glucose pattern. Both FVIII:c (r=0.69, p=0.03) and vWF:RiCof (r=0.69, p=0.006) were significantly correlated with the mean glucose levels. Correlation coefficients of F1+2 (r=0.58, p=0.07) and vWF:Ag (r=0.59, p=0.06) had borderline significance.

DISCUSSION

In this observational study, we have demonstrated how plasma glucose levels increase in response to hip replacement surgery. Following this rise in glucose, FVIII:c, vWF:Ag, vWF:RiCof and F1+2 levels also increased. These changes in mean glucose levels and mean levels of coagulation parameters during hip replacement surgery were closely correlated. All measured parameters remained elevated for several days up to seven weeks postoperatively. The link between glucose increase and activation of the coagulation system has been established before. Stegenga and co-workers showed in clamp studies that hyperglycaemia leads to upregulation of coagulation parameters in healthy volunteers, measured by soluble tissue factor and thrombin-antithrombin complexes.[3] Furthermore, exposure to prolonged hyperglycaemia (diabetes mellitus) is an established risk factor for VTE.[10] Coagulation activation by hyperglycaemia may be explained by mechanisms such as glycocalyx damage, non-enzymatic glycation, or the development of increased oxidative stress.[10,11] From the present study we cannot conclude whether increasing glucose levels directly activates the coagulation system. Activation of coagulation could be due to other causes such as vascular damage and bleeding induced by the surgery. However, it is of interest to note that the rise in glucose levels precedes the increase in the measured coagulation parameters and is closely correlated with these parameters. Our study was limited by the small sample size (n=9). This was therefore a pilot study, to determine whether hip surgery does indeed cause hyperglycaemia and whether this is associated with activation of the coagulation system. To investigate the direct influence of perioperative glucose levels on coagulation parameters, a randomised controlled trial is needed, comparing an intervention group in which normoglycaemia is maintained with untreated controls, as in our study population.

A consideration in interpreting the results is the possible lowering of coagulation parameters in response to the use of thromboprophylaxis and anticoagulants, especially the use of oral anticoagulants in three patients and the influence on F1F2. However, one would have expected an even larger increase in the coagulation parameters when no anticoagulants or thromboprophylaxis were used, and this is therefore not likely to have biased the results.

Glucose values were measured both fasting (preoperatively) and non-fasting (perioperatively). In the analyses we have attempted to overcome this limitation by comparing the non-fasting samples to the baseline mean glucose values and the fasting samples with the pre-induction sample. It should also be noted that the medium in which the blood was collected, trisodium citrate, is not the medium of choice for glucose measurements. We have, however, corrected for the dilution factor. In addition, samples were stored in ice-cooled tubes which were centrifuged immediately. This limits possible glycolysis.

In conclusion, our observations indicate that total hip replacement surgery causes glucose levels to increase, prior to a rise in the concentration of the measured coagulation parameters. This suggests a possible role of glucose in the activation of the coagulation system during hip surgery. Confirmation of this observation in interventional studies is needed.

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CASE REPORT

Splenic rupture following colonoscopy, a rare complication

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ABSTRACT

Splenic rupture is an extremely rare complication of colonoscopy. So far, less than 80 cases have been reported worldwide since 1970. We report two patients, one patient presenting with haemorrhagic shock after a therapeutic colonoscopy and another patient presenting with abdominal pain following a diagnostic colonoscopy. In both cases splenic rupture was diagnosed by abdominal computed tomography (CT scan). One patient was treated by selective embolisation of the splenic artery; the other patient underwent a splenectomy.

Because the numbers of colonoscopies performed in the Netherlands as well as in many other European countries are likely to double in the coming years as a result of the introduction of nationwide colorectal cancer screening programmes and intensive surveillance protocols after polypectomy, more splenic injuries as a complication of colonoscopy can be expected in the near future. Awareness of this complication is of great importance in early recognition and management of this potentially life-threatening injury.

KEYWORDS

Colonoscopy, complications, splenic injury

INTRODUCTION

According to Magma, the magazine of the Dutch Society of Gastroenterologists, 116,815 colonoscopies and 70,049 sigmoidoscopies were performed in the Netherlands in 2004.[1] One may assume that this number has increased over the past few years. This increase is partly due to intensive surveillance after polypectomy and screening programmes for hereditary and familiar colorectal cancer. It can be expected that the number of colonoscopies will increase even further in the future, certainly when in due course a national screening programme for colorectal cancer is introduced.[1]

Colonoscopy is a relatively safe diagnostic and therapeutic procedure. In general the procedure, with or without sedation, is well tolerated and the risk for serious complications is low.[2] The most frequent complications of colonoscopy are haemorrhage and gastrointestinal perforation, usually related to therapeutic interventions, such as polypectomy. The incidence of haemorrhage is 1 to 2% and the incidence of perforation is 0.1 to 0.2%.[2,3]

Less commonly described complications include pneumothorax, pneumomediastinum, volvulus, hernia incarceration, retroperitoneal abscess and emphysema, bacteraemia, endocarditis, vasovagal reaction, and bronchospasm.[2,4]

Splenic rupture is a very rare complication with an estimated incidence of 0.004% in all colonoscopies performed. A splenic rupture is a dangerous complication, with potentially lethal consequences.[4,5] The patient usually presents within 24 hours after the procedure with left upper quadrant abdominal pain, sometimes accompanied by shoulder pain.

We describe two patients who recently underwent a colonoscopy in our hospital, complicated by splenic rupture.

CASE REPORTS

Case 1

An 81-year-old man was admitted to the hospital because of abdominal pain and diarrhoea, without rectal haemorrhage, since he started using paracetamol-codeine and naproxen.

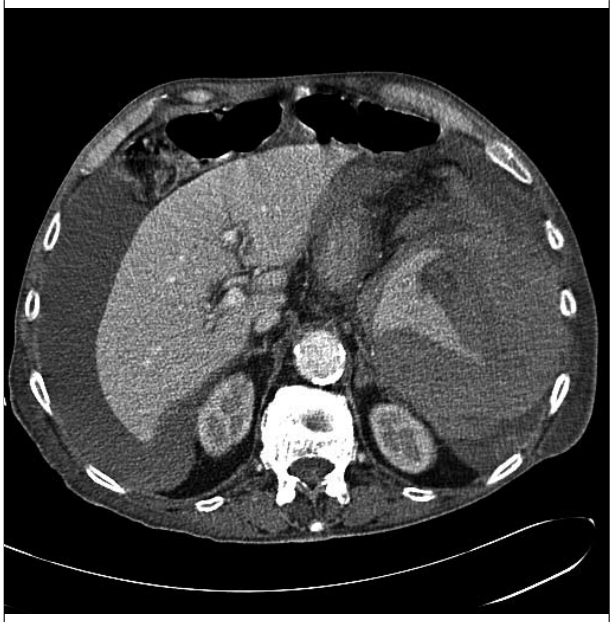
His medical history was significant for hypertension, chronic obstructive pulmonary disease, atrial fibrillation, benign prostatic hyperplasia and chronic back pain. His medication consisted of phenprocoumon, furosemide, tamsulosin, paracetamol-codeine, amiodarone, theophylline, acetylcysteine, naproxen, pantoprazole and macrogol.

The differential diagnosis included constipation with paradoxal diarrhoea, diverticulosis or colorectal cancer.

A diagnostic colonoscopy was performed. At admission, the phenprocoumon was stopped and the international normalised ratio (INR) was normal at the time of the colonoscopy. The examination was conducted without any difficulties. The caecum was unremarkable, but the colon showed severe diverticulosis, more pronounced in the left colon, and in the ascending colon a small sessile adenomatous polyp was found and removed. In the sigmoid, about 30 cm from the anus, a second pedunculated adenomatous polyp, with a diameter of 2 cm, was found and removed after injection of 2 cc of adrenaline 1:10,000. After the colonoscopy phenprocoumon was resumed. Thirty-six hours after the examination the patient was seen on the hospital ward because of dizziness. Physical examination revealed hypotension (80/40 mmHg) with a pulse rate of 70 beats/min, normal heart sounds and a prolonged expiration, without wheezing or crackles. The abdomen showed no peritoneal signs. Laboratory tests revealed a decrease in the haemoglobin from 6.8 mmol/l to 3.5 mmol/l and an INR of 5.86. The patient received a blood transfusion with five units of packed red cells, the prothrombin time was corrected to within the normal range with prothrombin complex concentrate and the phenprocoumon was stopped again. A retroperitoneal haematoma was considered, and an ultrasound of the abdomen was performed. The ultrasound demonstrated free fluid in the abdominal cavity and a pathological spleen. An abdominal computed tomography (CT) scan revealed a large haematoma in the spleen and massive intra-abdominal free fluid (*figure 1*).

Due to his medical history and clinical condition it was decided to perform a splenic embolisation. Haemostasis was achieved by selective embolisation of the splenic artery and placement of coils (*figures 2A* and *B*). After the procedure the patient was transported in a stable condition to the intensive care unit. At first his clinical condition improved. Later he developed respiratory insufficiency due to an exacerbation of chronic obstructive pulmonary disease (COPD). The chest X-ray showed no signs of redistribution or signs of transfusion-related acute lung injury (TRALI), pulmonary embolism, and acute myocardial infarction could be excluded. The patient was intubated and mechanically ventilated and treated with antibiotics and steroids. Nevertheless he died six days after the embolisation. No obduction was performed.

Figure 1. *Abdominal CT-scan with intravenous contrast*



Massive amount of free fluid in the upper abdomen. The spleen is deformed and shifted due to a haematoma.

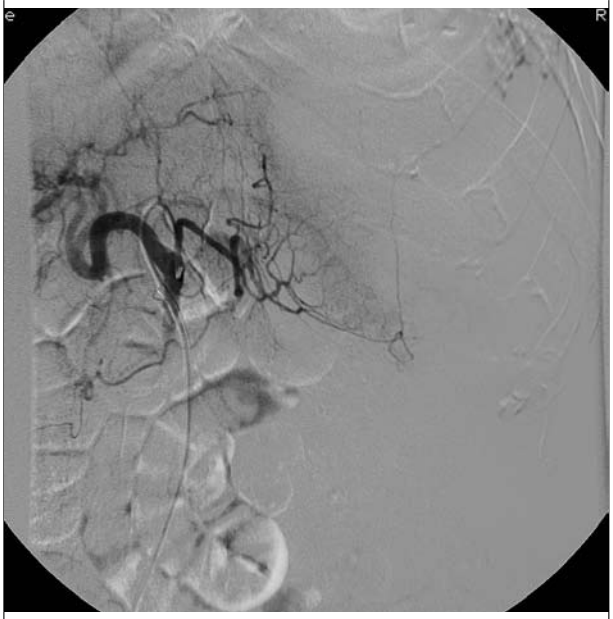
Case 2

A 66-year-old woman presented at the outpatients clinic with a change in her bowel habits. Her medical history was significant for a cerebrovascular accident, aneurysm of the abdominal aorta of 5.5 cm and hypertension. She was taking acetylsalicylic acid, triamterene and nebivolol.

A diagnostic colonoscopy was performed; the examination was unremarkable to the caecum, no biopsies were performed. The next morning she presented at the emergency room with left upper quadrant abdominal pain. The pain started the evening before and was progressive. At physical examination a pale woman was seen, with a blood pressure of 86/65 mmHg and a regular pulse rate of 55 beats/min. Auscultation of heart and lungs revealed no abnormalities. Abdominal examination showed a protuberant abdomen with hypoactive bowel sounds and normal span of liver dullness. There was pain on palpation in the hypogastric region without rebound tenderness. On presentation the haemoglobin level was 7.6 mmol/l, clotting profile was normal, as were liver functions, kidney function and electrolytes. A chest X-ray was unremarkable and a plain abdominal X-ray showed moderate dilation of the colon, with gas in the ascending colon but no free air.

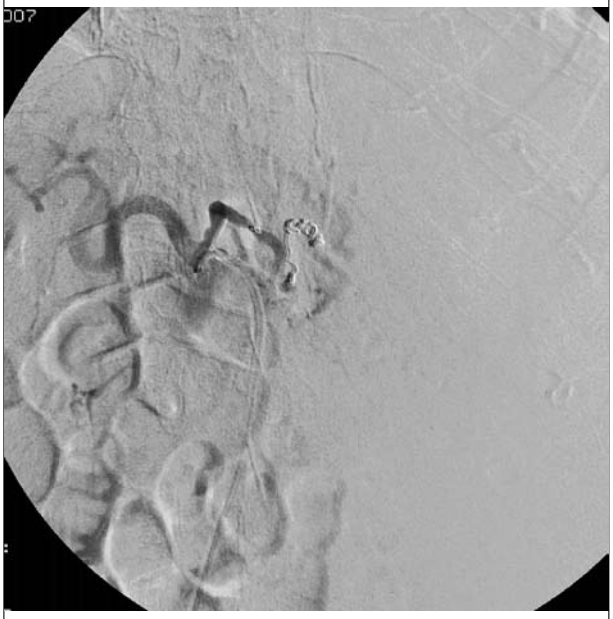
The differential diagnosis included a ruptured aneurysm of the aorta, and an abdominal CT scan (*figure 3*) was performed. The CT scan revealed a large intra-abdominal haemorrhage in the spleen region, in the paracolic recesses and in the pouch of Douglas, the spleen was no longer recognisable. No signs of rupture of the known aneurysm of the aorta were seen.

Figure 2A. *Selective angiography of the celiac trunk before embolization*



Because of the splenic artery is more narrow compared to the hepatic artery. The spleen is shifted medial due to haematoma.

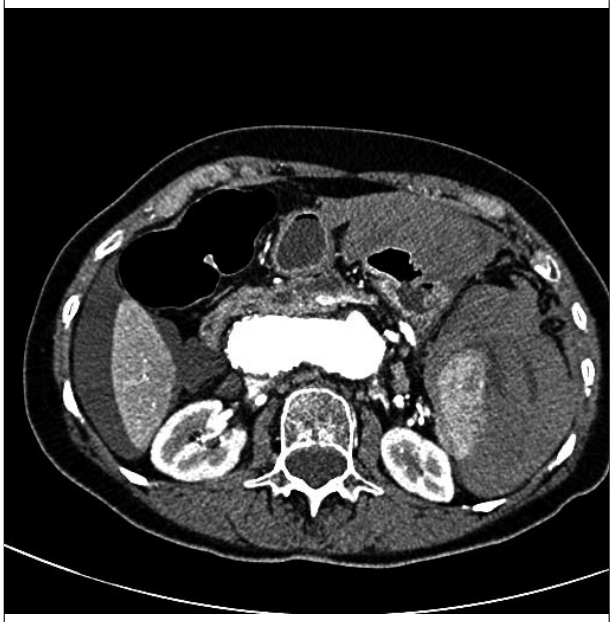
Figure 2B. *Selective angiography of the celiac trunk after embolization*



After the placement of several coils in the mid and distal part of the splenic artery there is stasis of the flow in the spenic artery.

The patient was transported to the intensive care unit. The haemoglobin decreased to 5.0 mmol/l. A splenectomy was performed and shortly after she was transported to the intensive care unit. In total she needed six units of packed red cells. The postoperative course was uneventful, pneumococcal vaccination was given and she was discharged home after a few days.

Figure 3. *Abdominal CT-scan with intravenous contrast*



Massive amount of free fluid in the upper abdomen. The spleen is deformed and shifted medial due to the haematoma. Known aneurysm of the abdominal aorta with elongation. No signs of rupture of the aneurysm.

DISCUSSION

Splenic rupture is a rare but dangerous complication of colonoscopy, with an incidence of 0.004%, and can be lethal.[4,5] The first report of splenic rupture as a complication of colonoscopy was described by Wherry and Zehner in 1974.[6] Since then, more cases have been reported.[1-5,7-11]

Clinical manifestation

Signs of splenic rupture usually occur within 24 hours after colonoscopy, but occasionally several days after the procedure.[3,4] The majority of patients present with abdominal pain in the left upper quadrant, with possible radiation to the left shoulder and peritoneal signs. Patient A did not fit this description, he did not present with abdominal pain and at presentation a splenic rupture was not suspected. An intra-abdominal haemorrhage was considered when the laboratory tests showed a significant decrease in the haemoglobin level without visible blood loss. Patient B did present with abdominal pain, but at first the pain was not in the left upper quadrant, but in the lower abdomen.

Pathogenesis

The exact reasons for developing a subcapsular or intra-parenchymal haematoma after a colonoscopy are not entirely clear although three mechanisms have been described. First, a direct trauma of the spleen when the endoscope passes through the splenic flexure has been suggested. Biopsy in the splenic flexure can also cause direct trauma of the spleen.[2,5,7,12] Second, rupture of the splenic capsule due to traction on the splenocolic ligament during

the colonoscopy, leading to haemorrhage, is mentioned. Third, rupture of the splenic capsule due to traction on the adhesions between the spleen and the colon could be the cause of splenic injury; these adhesions can be a result of prior operations, inflammation or infection.[2,5,7,12]

Risk factors

Risk factures for developing a splenic rupture during colonoscopy are splenomegaly, inflammatory bowel disease, oral anticoagulation therapy, difficult procedure, therapeutic procedures during the examination and intra-abdominal adhesions due to prior intra-abdominal surgery, inflammation or infection.[5,6,12]

None of these risk factors were present in these two reported cases. There were no difficulties in reaching the caecum in either of the patients. Indeed patient A was taking oral anticoagulation, but when the colonoscopy was performed his INR was normal and the polyps removed in patient A were not in the region of the splenic flexure. However, the INR was markedly elevated at time of presentation with the splenic rupture and this could have been significant.

Diagnosis

An abdominal CT scan is the diagnostic examination of choice to diagnose a splenic rupture.[2,4,7,12] A CT scan provides an estimate of the extent of the injury and can identify signs of haemoperotineum.[7] An abdominal CT scan, elaborated with contrast, provides an estimate of the activity of the haemorrhage and injury of the parenchymatous organs.[2] In stable patients a CT scan may help to decide whether the patient needs emergency surgery or can be treated conservatively.[7,12] In unstable patients, in whom a CT scan is not an option, an abdominal ultrasonography can be useful for quickly identifying free fluid in the abdomen.[12]

Therapy

There are three treatment options for a splenic rupture. The degree of splenic injury and the medical condition of each individual patient should be taken into consideration when deciding which treatment to use.[5] In a stable patient with an active haemorrhage, operative treatment by means of splenectomy is the treatment of choice.

Theoretically, spleen preserving surgery, by wrapping the spleen in a vicryl® net, is an option. Hypovolaemic shock is often present and after stabilising the patient splenectomy is in most cases the best solution.[5]

In a patient with active haemorrhage, another treatment option is selective embolisation of the splenic artery. During a catheter-guided angiography coils are placed in the splenic artery.[5] Sometimes embolisation particles are used or a combination of both. Angiographic embolisation is a good option in unstable patients with a high perioperative risk.

When the subcapsular haemorrhage is limited, conservative treatment is an option. In unstable patients, patients with pre-existing splenic disease (for example splenomegaly) or in case of a haemoperotineum this is not an option.[7]

CONCLUSION

It can be expected that the number of colonoscopies will increase in the future. This is due to intensive surveillance after polypectomy, screening programmes for hereditary and familiar colorectal cancer and the possible introduction of a nationwide screening programme for colorectal cancer.

Nowadays, the procedure is frequently performed with sedation to make it more tolerable. A disadvantage of performing the procedure with sedation is that the patient cannot inform about pain and thus possible signs of complications can be missed.

Of course, all patients should be well informed about the possible complications of the procedure. They should be given instructions about what to do if they experience symptoms after the procedure. Since the number of colonoscopies will increase in the future, there will also be more complications.

When a patient presents with abdominal pain and peritoneal signs or with signs of haemodynamic instability, with or without an acute fall in the haemoglobin level, a splenic rupture as a complication of colonoscopy should be considered.[2,12] Early recognition of the symptoms is of great importance in preventing a possible lethal outcome. An abdominal CT scan is the diagnostic imaging method of choice.

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CASE REPORT

Laryngeal manifestations of haemochromatosis

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ABSTRACT

We present a case with sudden onset of throat pain, dysphagia and hoarseness. On endoscopic examination, supraglottic swelling and a brown covering of the mucous membranes were seen. The diagnosis of haemochromatosis was made on laryngeal biopsy. The patient admitted to long-term iron treatment for anaemia. Haemochromatosis can affect many different organs. If the larynx is involved, the airway may be endangered.

KEYWORDS

Anaemia, airway obstruction, haemochromatosis, laryngeal

What is known on this topic?
Haemochromatosis can be primary (genetic) or secondary to excessive iron intake. Different organs may be affected. When symptoms occur, they are often non-specific, and result from iron overload in the organs. The disease is often discovered as an incidental finding. Screening tests are transferrin saturation and serum ferritin. Standard treatment is repeated phlebotomy or iron-chelating agents.

What does this add?
Involvement of the larynx by haemochromatosis has not been previously described. It is unclear in this case whether it was an incidental finding, or whether it contributed to the acute respiratory distress. If the former is true, this implies that routine laryngeal examination may be necessary in patients with haemochromatosis to avoid the airway becoming endangered.

INTRODUCTION

Primary haemochromatosis results from a genetic defect causing iron overload in various organs,[2,7] by increasing absorption of iron from the upper gastrointestinal tract.[2,5,8] The condition remains asymptomatic for several decades, until signs of end-organ disease develop. Symptoms are often non-specific in nature, and reflect the organs which are affected by iron deposition. Secondary haemochromatosis results from iron build-up in the organs from excessive intestinal iron absorption.[8]
Haemochromatosis is sometimes discovered as an incidental finding, on a routine blood test. Symptoms of haemochromatosis usually reflect the end organ involved. We describe the first case of haemochromatosis manifesting with laryngeal symptoms.

CASE REPORT

Mr A., a 73-year-old man, was admitted to our department with a history of a sudden onset of throat pain, difficulty swallowing and hoarseness. He had not previously suffered from hoarseness, any other throat symptoms or heartburn, was a non-smoker and did not drink alcohol regularly. He had a history of hypertension, ischaemic heart disease, chronic renal failure and type II diabetes mellitus. His regular drug treatment included antihypertensive drugs, diuretics, and iron, which he had taken for many years. On examination, he was afebrile, did not have increased skin pigmentation, had a hoarse voice, but showed no breathing difficulties. Endoscopic examination of the larynx revealed supraglottic oedema, which did not allow examination of the vocal cords. Blood tests were within normal limits, except for haemoglobin 11.43 g/dl (13.5 to 17.5), mean cell volume 88.4 (80 to 100), urea 39.6 mmol/l (2.5 to 7.5), creatinine 262.5 µmol/l (71 to 127), and ferritin 1107.8

µmol/l (40 to 562). Transferrin saturation was 19.9% (17.7 to 31.5). A provisional diagnosis of supraglottitis was made, and intravenous antibiotics and corticosteroids, and corticosteroid inhalations were started. After a few days of treatment, when the oedema had subsided, a dark brownish discolouration of the glottic and supraglottic mucous membranes was noted (*figure 1*). On direct laryngoscopy under general anaesthesia, dark brown patches were seen to be covering the supraglottis and vocal cords. Laryngeal biopsies were taken. Histology showed extensive perivascular iron deposits and iron incrustations (*figure 2*). To our knowledge, this is the first report in the literature of haemochromatosis presenting in the larynx.

Figure 1. *Brown deposits around the larynx and vocal cords, seen on direct laryngoscopy (254 x 203 mm)*

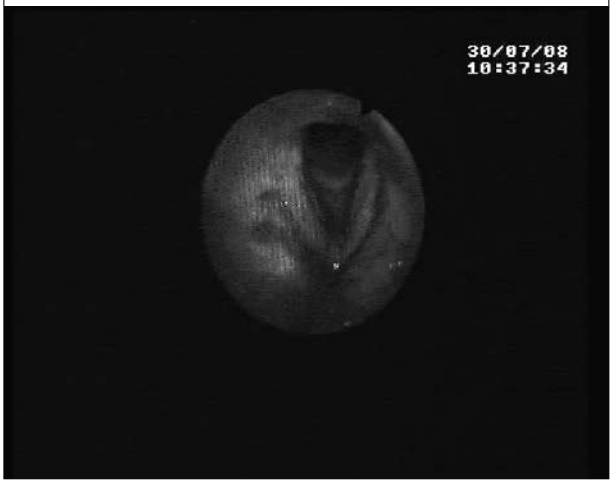
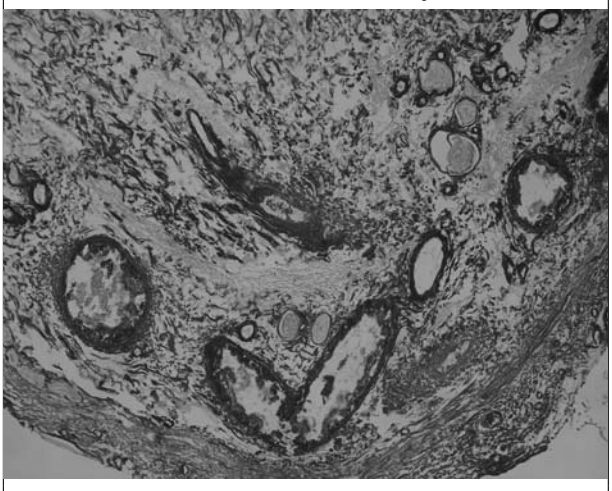


Figure 2. *Histology (iron stain x 100) showing extensive perivascular iron deposits and iron incrustations, on the connective tissue fibres*



The iron pigment deposits are stained blue with the iron stain (903 x 677 mm).

DISCUSSION

Our patient presented with an unusual manifestation of haemochromatosis in the larynx.

Chronic iron overload can be classified as primary or secondary haemochromatosis.[8] Primary haemochromatosis is an autosomal recessive genetic defect of the iron metabolism, causing increased absorption of iron from the duodenum and upper intestine.[2,5,7,8] It is a common genetic disease in Caucasians, and is caused by homozygous inheritance of an abnormality on the short arm of chromosome 6.[2,4,5,7] In most cases, the patients are homozygous for the C282Y mutation on the HFE gene.[2,3,6] Symptoms from haemochromatosus usually begin between 30 and 60 years of age. In secondary haemochromatosis, excess iron builds up from increased gastrointestinal absorption resulting from a defect of erythropoesis, iron tablets, diet, or multiple blood transfusions.[8] Since the body cannot excrete it, excess iron is deposited in various parenchymal organs.[2,5] Laryngeal deposits have so far never been described. If the diagnosis is not made early enough, irreversible end-organ damage is caused. Common screening blood tests are transferrin saturation and serum ferritin.[6,7] Liver biopsy used to be considered the gold standard for diagnosing this condition, but its use has been reduced recently by a combination of magnetic resonance imaging and genetic testing.[1,7] The disease may be asymptomatic. Clinical features are often non-specific, but when organ damage occurs, abnormal liver function tests, cirrhosis, diabetes mellitus, arthropathy, pancreatitis, cardiomyopathy, adrenal insufficiency, skin pigmentation, or testicular or ovarian atrophy can occur.[2,5,7] If the condition is recognised early and treated by regular phlebotomy or by iron chelating agents, irreversible complications can be prevented. Early detection and treatment before the onset of cirrhosis or diabetes mellitus, reduce morbidity, and a normal life-span can be expected.[2,5,7]

One of the first descriptions of haemochromatosis was of 'bronze diabetes',[4] describing the skin pigmentation. This is similar to the pigmented layer that we found on the larynx in our patient.

Care should be taken only to give iron treatment if it is indicated for iron deficiency anaemia, and only for the time necessary to correct the deficiency. Some patients also take over-the-counter vitamin preparations containing iron, and fail to mention them when asked about their drug treatment.

In our patient, the diagnosis of haemochromatosis was made histologically from laryngeal biopsies. It is unclear in this case if laryngeal haemochromatosis was just an incidental finding, or the cause of the episode of acute supraglottitis. Since the latter cannot be ruled out, the possibility of acute laryngeal inflammation should always

be borne in mind in patients with haemochromatosis, especially when discoloured brown or dark mucosal patches are present, in view of the risk of endangering the airway.

CONCLUSION

This is the first report of a laryngeal presentation of haemochromatosis. This condition is often asymptomatic, but if it is not diagnosed in time, end-organ disease may occur. Iron therapy should only be prescribed to patients with genuine iron deficiency, and only continued for the time required to correct the deficit. In patients with haemochromatosis, the possibility of laryngeal manifestations should be borne in mind, since these may include laryngeal oedema, which can endanger the airway.

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CASE REPORT

Fatal pneumonitis after treatment with docetaxel and trastuzumab

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ABSTRACT

Pneumonitis is a rare but serious complication of docetaxel treatment. We report a 63-year-old woman with locally advanced breast cancer who was treated with docetaxel and trastuzumab. After the first course she was admitted with febrile neutropenia that resolved rapidly. After the second course she was admitted again with fever and dyspnoea. Despite intensive treatment she died of respiratory failure three weeks later. Autopsy showed diffuse interstitial inflammation of both lungs consistent with drug-induced inflammation. Docetaxel treatment was the most likely cause. It is important to be aware of this toxicity, because the subtle warning signs can easily be mistaken for an opportunistic infection, and, if not recognised in time, the mortality rate is high.

KEYWORDS

Docetaxel, pneumonitis, pulmonary toxicity.

INTRODUCTION

Docetaxel is a chemotherapeutic agent that is increasingly used in the treatment of multiple types of cancer. Currently it is registered for breast cancer, non-small-cell lung cancer, head and neck cancer, gastric/lower oesophageal cancer and prostate cancer. The main side effects of docetaxel are neutropenia, hypersensitivity reaction, stomatitis, peripheral neuropathy and fluid retention. Pneumonitis is a rare side effect, but awareness of this toxicity is important, since the mortality rate is high. Because of expanding indications for docetaxel treatment, we expect an increase in the incidence of pneumonitis.

Trastuzumab is used in adjuvant and palliative treatment of breast cancer and has also been associated with interstitial pneumonitis, but in even fewer patients and less convincingly, despite large-scale use.

CASE REPORT

A 63-year-old female patient was diagnosed with inflammatory breast cancer of the right breast with extensive axillary and supraclavicular lymph node involvement, staged cT4N3M0. Her2/neu was overexpressed in the primary tumour. Oestrogen and progesterone receptors were negative. Neoadjuvant treatment with docetaxel (100 mg/m^2) and trastuzumab (6 mg/kg) once every three weeks was started. One week after the first course, she presented at the emergency department with fever (39.4°C), chills and minimal dyspnoea. Physical examination was otherwise unremarkable. A chest X-ray was normal. Laboratory examination showed transient leucocytopenia (1.1 x 10^9/l). She received intravenous ceftazidime and recovered rapidly. Blood and urine cultures remained negative. After five days she was discharged from the hospital.

During the second course, the patient received ciprofloxacin as antibiotic prophylaxis. On the sixth day she returned to the emergency room with fever, chills and dyspnoea. She had not experienced any chest pain, productive cough, dysuria or other localised symptoms in the previous days. Physical examination showed tachycardia and minimal basal lung crackles. A reduction in breast inflammation and in the size of loco regional lymph node involvement was noted. Her leucocyte count was 0.9 x 10^9/l and C-reactive protein (CRP) was 32 mg/l. Again, the chest X-ray showed no abnormalities. We suspected an upper respiratory tract infection and started broad-spectrum antibiotics. The fever and dyspnoea improved and the patient was discharged on the fourth day with oral antibiotics.

Four days later she was readmitted with fever (40.1°C), dyspnoea and a dry cough. Physical examination revealed fine crackles over both lungs, especially on the left side. A chest X-ray showed a consolidation in the lower lobe of the left lung. Leucocyte count was 6.1 x 10^9/l and CRP 51 mg/l. Amoxicillin/clavulanic acid and erythromycin were given, being the standard regimen in our institution for severe

community acquired pneumonia. Blood and urine cultures remained negative. The fever and dyspnoea persisted. Pulmonary embolism was excluded. Two days later she became tachypnoeic and oxygen saturation dropped to 65%. She was transferred to the intensive care unit and artificial ventilation was necessary. A thoracic computed tomography (CT) scan showed multiple consolidations in the peripheral parts of both lungs and ground glass aspect of lung lobuli indicating inflammation and/or oedema. A blood culture showed coagulase negative staphylococci and the antibiotic regimen was changed to vancomycin and ceftazidime. Broncho-alveolar lavage showed no microbiological pathogens in direct staining and cultures remained negative. Prednisone treatment was started, after which the fever disappeared, but her pulmonary situation worsened steadily. After nine days, adequate oxygenation became impossible. Treatment was stopped and the patient died instantly.

At autopsy heavy (2140 g), oedematous and firm lungs were found. Histological examination showed diffuse alveolar damage and interstitial inflammation of both lungs and pneumonic consolidations in the right lung. Small islands of invasive adenocarcinoma were demonstrated microscopically in the right breast and regional lymph nodes. Distant metastases were not found.

DISCUSSION

Pneumonitis is a rare side effect of docetaxel. In the past decade, several case reports and small case series of docetaxel-induced pneumonitis were reported. Almost 50% of reported patients died because of respiratory failure, usually after two to four courses of chemotherapy.[1-6] More recently, clinical trials have been published on the use of docetaxel in the treatment of non-small-cell lung cancer. Several studies showed patients developing grade 3-4 drug-induced pulmonary toxicity when using docetaxel in combination with different chemotherapy schedules or radiotherapy.[10-13] Pneumonitis rates as high as 7 to 10% occurred especially during or after concurrent radiotherapy.

The diagnosis of drug-induced pneumonitis may be obscured, as was probably the case in our patient, by the administration of high-dose dexamethasone (8 mg twice daily for three days) with each course of docetaxel. Corticosteroids in this dose range will suppress early signs of pneumonitis for several days. The subsequent appearance of fever and dyspnoea due to pneumonitis may coincide with the time period of neutropenia, leading to an erroneous diagnosis of neutropenic fever due to an opportunistic infection. The lack of objective thoracic X-ray abnormalities, as in this case, is not uncommon, both in early drug-induced pneumonitis and in neutropenic fever from pulmonary origin. Potential clues in this case were the repetition of fever, dry cough and dyspnoea after both the first and second course of treatment and the presence of fine crackles over both lungs, despite normal thoracic X-ray examination. An increased awareness of possible drug-induced pneumonitis, which is the purpose of this case report, should lead to early consultation with a pulmonologist and evaluation by (high-resolution) CT scan instead of relying on X-ray examination. When docetaxel-induced pneumonitis is part of the differential diagnosis, docetaxel treatment should only be continued after thorough pulmonological examination.

The mechanisms of drug-induced pneumonitis are not well-understood.[7] Various mechanisms have been proposed. One hypothesis is that docetaxel may cause proliferation of cytotoxic T cells directed against a specific pulmonary antigen co-expressed by the tumour,[2] thus leading to a hypersensitivity type of lung damage. Alternatively, docetaxel might cause direct pulmonary damage through reactive oxygen metabolites. Finally, a pharmacogenetic variant or a dosing error might have led to excessive docetaxel exposure in our patient, but the grades of haematological and non-haematological toxicities encountered in our patient being within the normal range argue against this.

Our patient developed symptoms of mild dyspnoea and fever after the first and second course of docetaxel and trastuzumab. Chest X-rays were initially normal. Blood and urine cultures remained negative. She was treated twice for febrile neutropenia, and exhibited a clinical course within the expected range. It is noteworthy, though, that the clinical presentation on the two occasions was very similar. The third admission, however, four

Figure 1. *Lung tissue with broad interalveolar septa and influx of neutrophilic granulcytes with haemorrhage*

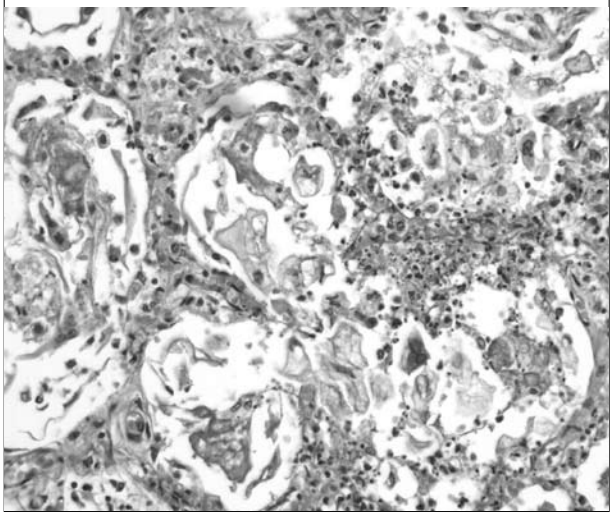
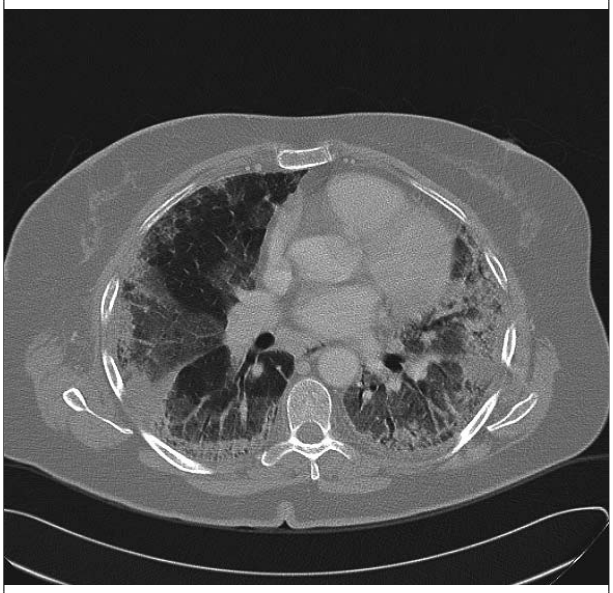


Figure 2. *CT scan showing bilateral airspace consolidations with ground-glass opacities in patchy distribution*



Small ill-defined centrilobular nodules. Predominance in middle and lower lung (205 x 205 mm).

days after the second discharge, should have provoked a wider differential diagnosis than non-neutropenic pneumonia. At that time, high-dose corticosteroids might have prevented the fatal outcome. In this case, prednisone was only started after negative bronchoalveolar lavage on the ICU. In retrospect, it is likely that the symptoms of dyspnoea and fever were, from the first episode, in fact signs of early interstitial pneumonitis. The clinical course and the findings at autopsy are entirely compatible with reported findings in patients with interstitial pneumonitis due to docetaxel.

Our patient was also treated with trastuzumab.[8,9] Trastuzumab-associated pneumonitis has been described, but data are far more sparse than for docetaxel. Just a few of the reported patients were treated with trastuzumab only. In contrast with docetaxel, trastuzumab-associated pneumonitis may develop many months after initiation of treatment and may run a more insidious course. In view of the extensive use of trastuzumab nowadays, trastuzumab-induced pneumonitis, if existent, seems rarer than docetaxel-induced pneumonitis. This leads us to conclude that the pneumonitis in our patient was due to docetaxel.

CONCLUSION

In summary, although pneumonitis is a rare side effect of docetaxel, it is an important to be aware of this specific toxicity, since the first manifestation may mimic an opportunistic pulmonary infection, but early recognition and appropriate treatment may be life saving. With the expanding indications of docetaxel, this side effect may be encountered more often in daily practice. Treatment consists of stopping docetaxel and starting corticosteroids.

ACKNOWLEDGEMENTS

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SPECIAL REPORT

Criminal prosecution for the death of patients

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The tragedy started after a seemingly insignificant call from the water distribution company. They informed me, the medical director of a small dialysis centre on the island of Curaçao, that an interruption of our water supply was scheduled. Haemodialysis centres require high volumes of water that is used for the dialysis treatment, so at first I welcomed this information. The scheduled interruption of water supply lasted several hours on 21 May 1996 (day 1) after which we did extra flushing of water to dispose of debris, changed the water filters and resumed haemodialysis treatment. The first signs of illnesses among the dialysis patients were noted more than three weeks later (day 25), when some patients had complaints of nausea and vomiting. Postdialysis hypercalcaemia was observed in 25 of the 28 patients. At that time the diagnosis 'hard water syndrome' due to a high dialysate calcium concentration was made when the water company indeed established a higher than usual calcium content in the water supply. The use of calcium and vitamin D supplements by the patients was stopped, but because the hypercalcaemia persisted in some patients, I closed the dialysis unit (day 40) and referred all the patients to the hospital for dialysis treatment. The symptoms of nausea, vomiting, as well as the hypercalcaemia disappeared after a single dialysis with low calcium dialysate. Nevertheless, unexpectedly, things only got worse and the following three weeks ten patients suffered severe progressive neurological symptoms with disorientation, myoclonus, convulsions and coma. Symptomatic treatment had no effect and these ten patients died from encephalopathy (day 40 to 95). Initially, no one had a clue what had caused this tragedy but after an extensive literature search it became obvious that the symptoms had to be caused by an outbreak of subacute aluminium intoxication due to an unusually high aluminium content of the water supply of the dialysis unit. The 18 survivors had only minor symptoms but had to be transferred to five dialysis clinics in the Netherlands for treatment.[1]

An investigation led by the health inspectorate, the water company and international water experts established the sequence of events. Patients on maintenance haemodialysis are parenterally exposed to 150 to 200 litres of water during each haemodialysis treatment. To ensure the water quality, water treatment systems with reverse osmosis filters have been used in most countries since the early 1980s. Some dialysis centres, however, continued using untreated tap water until the 1990s.[2] Curaçao, an island of the Netherlands Antilles, has no natural water resources and therefore its public drinking water supply depends totally on seawater desalination. Public city water was produced by distillation of seawater and had been used for haemodialysis without extended purification for more than 22 years in the local hospital. Therefore, no water treatment system was installed when the dialysis centre was opened in 1992. Because of corrosion problems, the ductile-iron pipes of the public city drinking water distribution mains were switched to other pipes with an inner layer of cement. Such a pipe was installed in the region that supplied the dialysis centre and a small shopping area. Aluminium and calcium are important constituents of cement. In this case the combination of a higher than usual aluminium content of the cement and a low calcium concentration of the tap water facilitated the leaching of calcium and aluminium from the cement-lining into the drinking water system of the dialysis unit, causing firstly the 'hard water syndrome' and because it takes time to develop after a delay in symptoms, secondly a subacute aluminum encephalopathy. Aluminium concentrations, first measured after the new cement-mortar pipe had been in use for six weeks, were 5 µg/l at the water plant and 690 µg/l at the dialysis centre.[3] Due to a tragic coincidence a new water treatment system that may have prevented the intoxication had been purchased, but installation was delayed for logistic reasons.

A criminal investigation was started and after an investigation by the local and Dutch Health Inspectorate, the Water Authorities from the Netherlands and the Pan American Health Organisation (invited by the government

because of the complexity of the case), the prosecutor initially decided to dismiss the case. After an appeal from the families of the patients who had died, the Court of Appeal, decided to pursue prosecution of my colleague and myself. Some patients also requested the prosecution of board members of the water utilities but at that time no legal provision was in force to allow this. From 6 June 1998 until January 1999 a preliminary judicial inquiry was performed in the Netherlands and on Curaçao. Thirteen experts were appointed by the investigative judge consisting of two water experts, two dialysis technicians and nine medical and nursing experts from four universities and three dialysis clinics on Curacao and in the Netherlands. After a cross-examination of the court-appointed experts by the prosecutor and the investigative judge, the prosecutor charged me of gross negligence and manslaughter for not testing the composition of the water after the construction at the water distribution network. A prison sentence with probation of six months was demanded. After a court hearing and a deliberation of ten hours, the District Court disagreed with the prosecutor on all issues, but nevertheless held me as the medical director guilty for performing dialysis without a water treatment system even though this was not an element of the charge. A prison sentence with probation of six months was demanded, together with the local maximum financial penalty (6500 US dollars) for these cases. My colleague was acquitted because he was not responsible for the water quality. I filed an appeal and in May 2000, the Court of Appeal held that it was not allowed to rule on the omission to install a water treatment system because this issue was not included in the charge and overturned the conviction.[4]

For all of us involved, including the medical staff, it was emotionally extremely difficult to deal with the death of the patients we all knew very well because of the frequent dialysis sessions. Another frustrating experience was the huge media coverage and the duration of the criminal prosecution that lasted four years. One of the main reasons to find strength emotionally was the fact that all the survivors showed enough confidence in the medical staff to return for treatment in the dialysis centre where they had been intoxicated. In my opinion the following actions may help health care workers who are being prosecuted for the death of patients:

1. Produce a detailed report early in the process in cooperation with legal and medical advisors. These written reports, prepared in advance of the legal procedures, can serve as forms of insurance and reassurance. It can be used as a private document or may be used in court. One should not deviate from the details in that report.
2. Avoid the media, or do a media training. Shortly after the tragedy I was questioned at a local radio station where I said things that did not help my case. I do not regret anything I said, but media training – which I did not do – probably would have improved the way things were said.
3. Avoid finger pointing. Preventable adverse events are often the result of failure of several points of a system and frequently several individuals are involved. System errors may be due to equipment failures or may be the result of inadequate reporting/communication, inadequate training or supervision of doctors/other personnel, inadequate staffing or record-keeping, etc. One should be very hesitant to blame others too openly, as this will probably backfire.
4. Do a thorough literature investigation of the issues involved. In this case I had to read all relevant literature on water production and distribution issues, aluminium intoxications and legal issues. The accused should become an active participant in the preparation of the case, critical to ensuring that his interests are properly protected. At trial he should have more knowledge and valid opinions about the case than the experts. It has an added benefit of reducing the psychological burden of standing helplessly by, while the verdict unfolds. In court one should have a thorough knowledge of all the details in the file. One should also know that the way a lawyer prepares a case may be the exact opposite of the way doctors approach a medical problem. Whereas a doctor looks for facts in order to reach a conclusion, a trial lawyer looks to the desired conclusion to determine what facts he needs to seek.
5. Try to understand the public opinion and the reason why you are being prosecuted. One of the few things an accused can do is to try and understand the litigation process in order to reduce the anxiety that comes from the course of the prosecution and ruling by the judges. The number of criminal prosecutions against physicians has been increasing in several countries.[5-10] This increase in the number of criminal prosecutions may be due to several factors. First, there is a growing concern about medical errors. Doctors, like lawyers and airline pilots, prefer to think of themselves as routinely hyper-careful people whose work habits do not permit error. Unfortunately, physicians are responsible for many accidental deaths[11] and in some cases this overconfidence may be a basis for medical errors in general, and diagnostic errors in particular.[12] Second, it may be costly for a plaintiff to initiate civil court litigation when it is not possible to have a lawyer that works on a no-cure no-pay base.[7] Third, the general opinion may be that medical licensing boards are ineffective in imposing sanctions against physicians for grossly negligent or incompetent behaviour as administrative sanctions against physicians may seem inappropriately related to the seriousness of the outcome. Letting a criminal court draw the line between acceptable medical performance and criminal

negligence may seem to offer advantages (e.g. courts are impartial; public trust could be helped by them holding doctors accountable). In these cases the public expects criminal prosecution to play a major role in assuring medical safety and prosecutors may conclude that criminal charges are the only way to protect the public. Unfortunately, it may be difficult for the criminal legal systems to draw a line between acceptable performance and negligence as prosecutors are not equipped to deal with medical issues. Therefore one should realise that it can take a long time, sometimes more than one year, for the police to only come to the decision whether to indict a physician.[4] In addition, criminal prosecution of practitioners has been shown to have overwhelmingly negative effects for these persons as they can become depressed and sometimes may be unable to work because of the stress.[5,11]

6. Seek psychological help, from professionals, colleagues, family or friends. Even before a doctor has gone to court, consequences of impending prosecutions spread themselves across them and their colleagues. The stress and isolation that practitioners can feel when subject to legal charges or a trial will be an enormous burden and it may be difficult to continue to carry out your jobs normally.
7. Exercise. Jogging has helped me a lot in distracting my mind from the psychological stress. A special goal, like running a marathon, can reduce the negative state you are in.
8. Write a publication of the incident. One may be very reluctant to write about one's (presumed) errors, because of shame or because we want to put it aside when the proceedings are over. However, other persons can make the same mistakes and therefore should be able to learn from similar incidents. Judicial proceedings, nevertheless, can create a climate of fear about sharing information.

For the medical practitioner, prosecution for the death of patients will be one of the most distressing experiences in their medical career, not only because the judicial process may last several years, but primarily because it touches upon the foundation of medical ethics as physicians do not intentionally cause harm. Certainly, prevention, by optimising patient's safety, remains the best way to avoid adverse outcome and criminal prosecution.

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PHOTO QUIZ

Acute abdominal pain in a patient receiving enoxaparin

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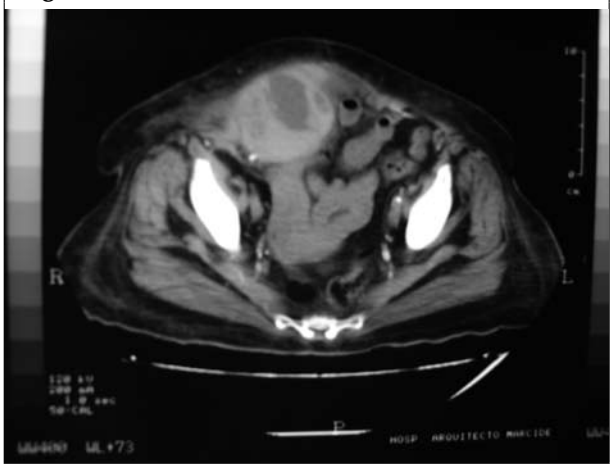
CASE REPORT

A 73-year-old woman with ischaemic heart disease, permanent atrial fibrillation, and chronic renal failure complained of a sudden onset of severe abdominal pain. She had been hospitalised 13 days earlier because of a head injury with impaired consciousness and periorbital haematoma. During that hospitalisation her treatment with acenocumarol was interrupted and enoxaparin, 60 mg subcutaneously every 12 hours, was administered. On physical examination, a tender mass was felt in the right lower abdominal quadrant. Laboratory analyses revealed the following: The haemoglobin level was decreased from 7.50 mmol/l to 6.2 mmol/l (normal 7.45 to 9.30 mmol/l), the partial thromboplastin time was 45 seconds (normal 22 to 37 seconds), the prothrombin time was 13 seconds (an international normalised ratio of 1.09), the serum creatinine level was 167.96 µmol/l (normal 50 to 110 µmol/l), and the estimated glomerular filtration rate value was 28 ml/min/1.73 m^2. A computed tomography scan (*figure 1*) was obtained.

Figure 1. *Abdominal CT scan*



WHAT IS YOUR DIAGNOSIS?

See page 244 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (ON PAGE 243)

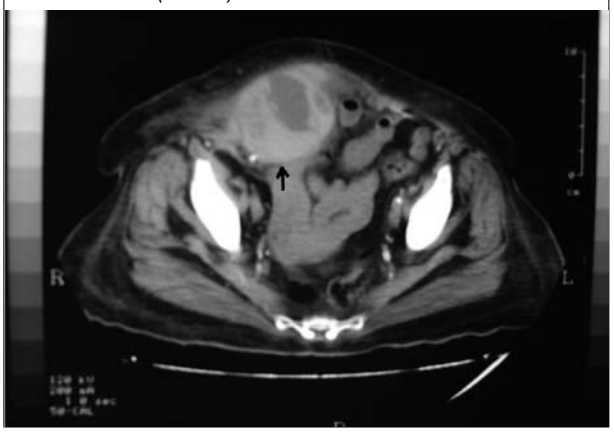
ACUTE ABDOMINAL PAIN IN A PATIENT RECEIVING ENOXAPARIN

DIAGNOSIS

The computed tomography scan showed a haematoma expanding in the lower half of the right rectus sheath (*figure 2*, arrow). Enoxaparin was discontinued, and the patient made a gradual clinical recovery with conservative treatment.

Rectus sheath haematoma is an uncommon but serious bleeding complication associated with, among other causes, anticoagulant and antiaggregant therapies. It may be misdiagnosed as appendicitis, cholecystitis, torsion of an ovarian cyst, or acute pancreatitis.[1] In cases following administration of enoxaparin subcutaneously into the abdominal wall, it can occur as a result of accidental direct damage to the muscle itself or to the epigastric vessels. Likewise, because renal function plays an important role in the clearance of enoxaparin, patients with renal insufficiency who are receiving therapeutic doses of enoxaparin have an increased risk for bleeding that may be attributable to an elevated level of anti-Xa. Thus, several authors[2] recommend a reduction in enoxaparin dosing in patients with a creatinine clearance lower than 30 ml/min. Our patient had severe renal failure which could contribute to her bleeding. Rectus sheath haematoma is managed conservatively in the majority of patients. Surgical intervention may be necessary with large haematomas with haemodynamic instability, and endovascular embolisation is a suitable alternative to surgical treatment in cases in which the haematoma continues to expand.[3]

Figure 2. *Computed tomography scan showing a haematoma (arrow) in the rectus sheath*



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Bilateral swollen eyelids occurring during adjuvant treatment with tamoxifen for early breast cancer

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CASE REPORT

A 56-year-old woman had been treated with surgery and radiotherapy for a pT1N2 hormone-receptor-positive lobular carcinoma of the left breast. She received adjuvant treatment with five cycles of FEC chemotherapy (5-fluoro-uracil, epirubicin and cyclophosphamide) and afterwards endocrine treatment with tamoxifen.

After seven months on tamoxifen, she presented to the dermatologist with oedema of the eyelids of both eyes, continuously present and progressive since several months. Previous treatment with antibiotics had not given any relief. Her vision was somewhat disturbed. She had no pain or other complaints. Angio-oedema due to tamoxifen was suspected. Treatment with antihistamines and prednisone was not helpful, nor was stopping the tamoxifen. The swelling was progressive and became indurated. Then a biopsy of the lower left eyelid was taken and the patient was referred to the internist. Besides the extensive swelling of the eyelids with slight red-blue discoloration of the skin (*figure 1*), there were no other abnormalities at physical examination.

WHAT IS YOUR DIAGNOSIS?

See page 246 for the answer to this photo quiz.

Figure 1. *Photo showing bilateral swollen eyelids, scar of biopsy left lower eyelid*

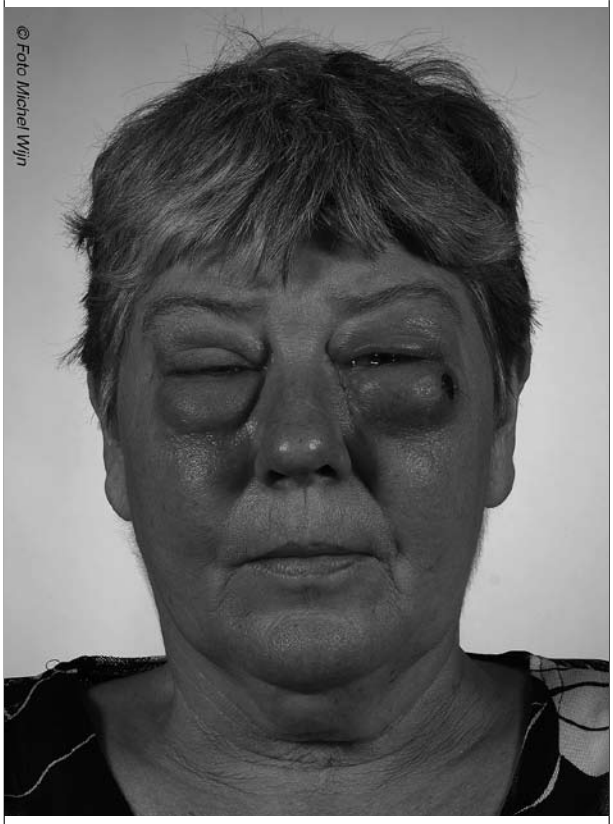


Photo is showed with permission of the patient.

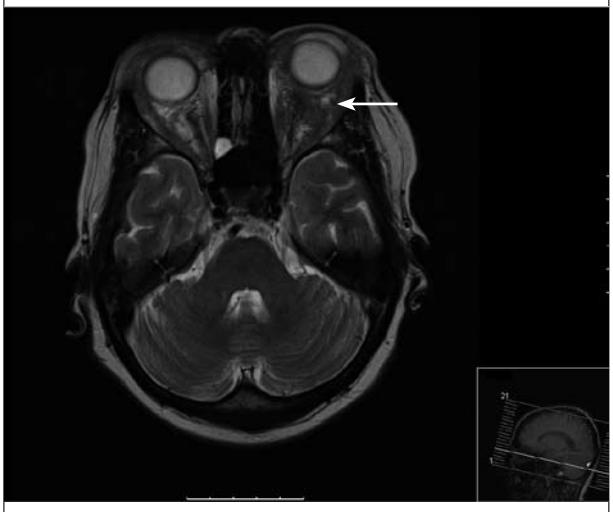
ANSWER TO PHOTO QUIZ (ON PAGE 245)

BILATERAL SWOLLEN EYELIDS OCCURRING DURING ADJUVANT TREATMENT WITH TAMOXIFEN FOR EARLY BREAST CANCER

DIAGNOSIS

The differential diagnosis of swollen eyelids encompasses infections (cellulitis, sinusitis, trichinosis), allergy, several forms of angio-oedema, hypothyroidism, Graves opthalmopathy, nephrotic syndrome and other causes of hypoalbuminaemia, malignancies, lymphoedema, cavernous sinus thrombosis and autoimmune diseases.[1]
In this patient most of these diagnoses could easily be excluded. The biopsy of the left eyelid showed subcutaneous metastases of adenocarcinoma, matching the earlier diagnosed breast cancer. An MRI scan showed orbital masses with contrast enhancement, which fitted with orbital metastases (*figure 2*).

Figure 2. *Axial T2WI MR of the brain showing bilateral orbital metastases*



Arrow indicates biggest soft tissue mass.

Further diagnostic work-up revealed diffuse skeletal, liver and peritoneal metastases.
Palliative chemotherapy with docetaxel was given. Unfortunately, the patient developed progressive systemic disease under this treatment. Palliative radiotherapy to both orbital contents (36Gy) did not give local relief either.
Orbital metastases were the first sign of disseminated breast cancer in this patient. The orbit is an unusual site for metastases. Several authors have reported their experience with metastases to the orbit in case reports. Breast cancer accounted for the majority of cases. Survival is usually limited due to other systemic metastases. Patients complained of blurred vision, diplopia and pain. A biopsy is necessary to confirm the metastatic nature of the lesion.[2] Treatment consists of hormonal therapy, chemotherapy or radiotherapy.

CONCLUSION

Swollen eyelids caused by orbital metastases as the first sign of metastasised breast cancer.

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PHOTO QUIZ

An unexpected cause of iron deficiency detected by capsule endoscopy

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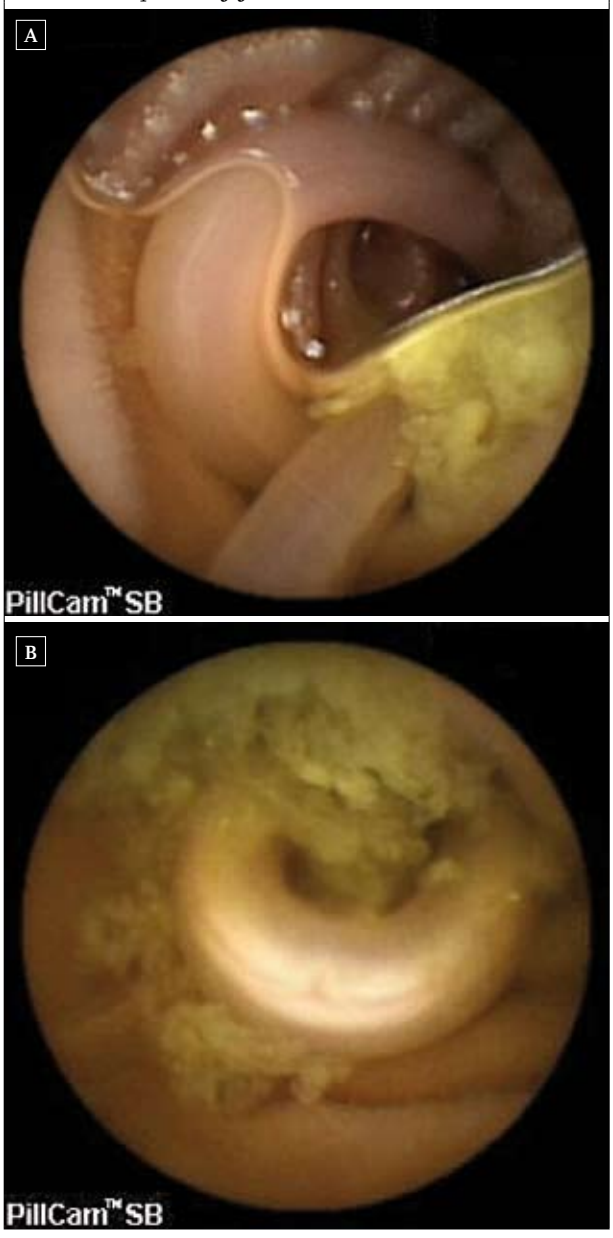
CASE REPORT

A 52-year-old woman was referred to our hospital for analysis of iron deficiency anaemia. Her medical history revealed extirpation of a meningeoma, Graves' disease and atrial fibrillation. She had no complaints. Physical examination was normal. Laboratory investigations revealed microcytic anaemia (haemoglobin 7.3 mmol/l, mean cell volume 76 fl) and iron deficiency (ferritin 15 µg/l, normally >30). Upper gastrointestinal endoscopy, including duodenal biopsies, and ileocolonoscopy were performed, revealing no abnormalities. A video capsule endoscopy was subsequently performed using the Given® system to evaluate the small bowel for a possible bleeding source. Capsule endoscopy revealed abnormal findings (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 248 for the answer to this photo quiz.

Figure 1. *Capsule endoscopy image showing an abnormality in the jejunum*



ANSWER TO PHOTO QUIZ (ON PAGE 247)

AN UNEXPECTED CAUSE OF IRON DEFICIENCY DETECTED BY CAPSULE ENDOSCOPY

DIAGNOSIS

Based upon the capsule endoscopy images, the diagnosis of ascariasis was made in this patient. Further laboratory investigations revealed a raised eosinophilic count of 5.5 x 10^9/l (normal <3.0 x 10^9/l) and an elevated level of total immunoglobulin E (456 kU/l, normal <115 kU/l). The patient was treated with mebendazole 100 mg twice daily for three days. The haemoglobin level gradually normalised and remained normal in the following years.

Ascaris lumbricoides, an intestinal roundworm, is one of the most common helminthic human infections worldwide.[1] The highest prevalence of ascariasis occurs in tropical countries where warm, wet climates provide environmental conditions that favour year-round transmission of infection.[2] Transmission occurs mainly via ingestion of water or food (particularly raw vegetables or fruit) contaminated with *Ascaris lumbricoides* eggs and occasionally via inhalation of contaminated dust. Adult worms inhabit the lumen of the small intestine, usually in the jejunum or ileum. They have a life span of ten months to two years and are then passed in the stool. The majority of infections with *Ascaris lumbricoides* are asymptomatic.[1] However, symptoms can occur as a result of direct tissue damage (manifested as occult blood loss in our patient) or due to an immunological response of the host to the infection with larvae, eggs or adult worms. Obstruction of the lumen of the gastrointestinal tract has been reported by an aggregation of worms.[3] In symptomatic patients, treatment is generally advised with anti-helminthic drugs.

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THE HIV TRIAL GUIDE

A guide to major studies, trials and acronyms of HIV antiretroviral therapy

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This guide provides the reader with a summary of published results of the major and important trials and studies of antiretroviral treatment in HIV-infected subjects (adults and children), from the 1st studies with zidovudine up to May 2007, including the 14th CROI in Los Angeles, USA, 2007.
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THE HEPATITIS TRIAL GUIDE

A guide to major studies, trials and acronyms of hepatitis B, C and D antiviral therapy

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The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs: Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

Keywords: Include three to five keywords in alphabetical order.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely, without discussion.

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Acknowledgement: All funding sources should be credited here. Also a statement of conflicts of interest should be mentioned.

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1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med. 2001;59:184-95.
2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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