Computer-Assisted versus Oral-and-Written History Taking for the Prevention and Management of Cardiovascular Disease: a Systematic Review of the Literature

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ABSTRACT

Background and objectives: CVD is an important global healthcare issue; it is the leading cause of global mortality, with an increasing incidence identified in both developed and developing countries. It is also an extremely costly disease for healthcare systems unless managed effectively. In this review we aimed to:

– Assess the effect of computer-assisted versus oral-and-written history taking on the quality of collected information for the prevention and management of CVD.

– Assess the effect of computer-assisted versus oral-and-written history taking on the prevention and management of CVD.

Methods: A systematic review of randomised controlled trials that included participants of 16 years or older at the beginning of the study, who were at risk of CVD (prevention) or were either previously diagnosed with CVD (management). We searched all major databases. We assessed risk of bias using the Cochrane Collaboration tool.

Results: Two studies met the inclusion criteria. One comparing the two methods of history-taking for the prevention of cardiovascular disease n = 75.

The study shows that generally the patients in the experimental group underwent more laboratory procedures, had more biomarker readings recorded and/or were given (or had reviewed), more dietary changes than the control group. The other study compares the two methods of history-taking for the management of cardiovascular disease (n = 479). The study showed that the computerized decision aid appears to increase the proportion of patients who responded to invitations to discuss CVD prevention with their doctor. The Computer-Assisted History Taking Systems (CAHTS) increased the proportion of patients who discussed CHD risk reduction with their doctor from 24% to 40% and increased the proportion who had a specific plan to reduce their risk from 24% to 37%.

Discussion: With only one study meeting the inclusion criteria, for prevention of CVD and one study for management of CVD we did not gather sufficient evidence to address all of the objectives of the review. We were unable to report on most of the secondary patient outcomes in our protocol.

Conclusions: We tentatively conclude that CAHTS can provide individually-tailored information about CVD prevention. However, further primary studies are needed to confirm these findings. We cannot draw any conclusions in relation to any other clinical outcomes at this stage. There is a need to develop an evidence base to support the effective development and use of CAHTS in this area of practice. In the absence of evidence on effectiveness, the implementation of computer-assisted history taking may only rely on the clinicians' tacit knowledge, published monographs and viewpoint articles.

KEYWORDS

history-taking; computer; cardiovascular disease; CVD; prevention; management

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BACKGROUND

Cardiovascular Disease (CVD) is caused by a disorder of the heart and circulatory system. In this review we are specifically looking at atherosclerotic cardiovascular disease which includes coronary heart disease, cerebrovascular disease (stroke) and peripheral artery disease. CVD is a leading cause of mortality globally. Chronic diseases, including cardiovascular disease, were estimated to cause more than 60% (35 million) of all deaths in 2005; more than 80% of these deaths occurred in low-income and middle-income countries (31). According to the 2010 Global Burden of Disease Study (58) ischaemic heart disease and stroke killed 12.9 million people in 2010, or one in four deaths worldwide, compared with one in five in 1990. The World Health Organisation projects that by 2030, almost 23.6 million people will die from CVD (10). The risk of developing vascular disease and the rate of its progression is determined by certain 'fixed' risk factors: age, sex, family history of vascular disease and ethnic groups, as well as by certain 'modifiable' risk factors: hypertension, hypercholesterolaemia, physical inactivity, obesity, tobacco consumption and diabetes (51). Ineffective management of CVD associated modifiable risk factors can lead to an increased risk of an adverse cardiovascular event. People with established CVD (such as angina pectoris, CHD, myocardial infarction, transient Ischaemic attacks, stroke or peripheral vascular disease) are at high risk of developing recurrent cardiovascular events; it is possible to prevent this by reducing a patient's cardiovascular risk by modification of adverse lifestyle behaviours and adhering to treatment, thus enabling effective management of their chronic condition (59, 33).

CAHTS facilitate automations of history taking approaches; hence aiding the collection of information in a timely manner by drastically reducing the time spent on dictating and collating written records, while being able to present relevant data in an easily accessible format (50, 4). They can also be administered at a time that is convenient to the patient and practitioner, saving resources, such as additional time and space (57, 30). Additionally, CAHTS can promote inter-operability between systems and compatibility with electronic health record templates (40). This offers the benefit that the information collected could be linked to a computerized decision support system which can offer patients personalized feedback on their lifestyle choices and advice on how to modify these to reduce their risk of developing or redeveloping cardiovascular related complications.

Clinician and patient-operated CAHTS may help to improve data quality through:

- data entry forms with data validation checks (for example erroneously entered information, such as age of 300, may lead to a prompt for the person to correct this;
- coding of data;
- eliminate transcription errors as the information is not dictated;
- legibility;
- easier access to past records; attribution of entries;
- greater availability;
- facilitating patient verification of their personal information.

Patients can also administer the CAHTS online and on lifestyle and self-generated biomarker readings (for example, blood pressure or blood cholesterol) can be shared with their clinician and assessed without the need for a face to face consultation. Additionally, collected information from gathered histories can generate data sets that may facilitate future epidemiological research (34).

CVD is an important global healthcare issue; it is the leading cause of global mortality, with an increasing incidence identified in both developed and developing countries. CVD is an extremely costly disease for healthcare systems and unless managed effectively, will continue to pose serious challenges to these systems and to the allocation of scarce resources (9). Evidence suggests that current programmes for cardiovascular management offer feasible, cost-effective ways to reduce CVD mortality and morbidity in both developed and developing country populations (10, 23); implementation of such programmes should thus be a priority for health policy-makers. With the move from hospital care to community-based care in many parts of the world, staff become increasingly mobile, thus require access to data input facilities at the point of care. If a patient's history were taken by a CAHTS, the information could be more accessible to the entire, multi-disciplinary, healthcare team and assist in the planning of an appropriate care package for the patient.

Most of the computer-assisted technologies are presently supported by limited empirical evidence. This impedes widespread adoption in the management and prevention of CVD, hence necessitating more evaluations of CAHTS. There is also a need for regular evaluations, analogous to techniques used in continuous quality improvement in healthcare (36, 1, 11). Unless these systems are adequately studied, they may not 'mature' to the extent that is needed to realise their full potential when deployed in every-day clinical settings (18, 15). Because only a few randomised controlled trials involving CATHS have been performed so far, it has been speculated that the improvements in the volume and accuracy of the answers seen in studies (34, 57, 24) may not accurately reflect the intervention. It has been suggested that the effects may be attributed to novelty and performance biases whereby the behaviour of researchers and patients was influenced (24).

CAHTS are frequently promoted as being 'cost-saving' (26, 45), yet cost-effectiveness and efficiency was rarely evaluated rigorously (37), therefore comprehensive cost-effectiveness analyses will be required to assess the financial rationale for choosing one CAHTS over another history taking tool, especially within disease management (45, 28). Although CAHTS have been available for around 50 years, successful use in routine healthcare remains variable. This review aims to establish whether these systems could be effective for the management of CVD, by assisting patient adoption of lifestyle modification behaviour and assisting treatment adherence, and identify any gaps in the research surrounding this. This systematic review involves an up-to-date literature search and detailed description of the studies on CAHTS to provide the framework for a comprehensive evaluation that will lead to an evidence base to inform policy and practice.

METHODS

TYPES OF STUDIES AND PARTICIPANTS

We considered RCT studies that included participants 16 years or older at the beginning of the study, who were at risk of CVD (prevention) and those who were previously diagnosed with CVD (management).

TYPES OF INTERVENTIONS

We considered the following six types of CAHTS:

1. Computer-assisted self-interviewing;
2. Audio computer-assisted self-administered interviewing;
3. Computer-assisted face-to-face interviewing;
4. Computer-assisted telephone interviewing;
5. Interactive voice response telephone interviewing;
6. Internet-based computer-assisted history taking.

CONTROL

Oral and written history taking for people with modifiable CVD risk factors (prevention) and those diagnosed with CVD (management).

OUTCOMES

Primary outcomes:

- Response rates to invitations for (lifestyle) assessment for CVD.
- Quality of data recorded (Composite outcome including: error rates, accuracy, reliability, completeness).
- Lifestyle modifications (Composite outcome including: changes in tobacco consumption (pack years), weight (kg), dietary intake (self-reported intake), physical activity level (number of days a week patient participates in physical activity); Biomarker reading modifications (Composite outcome including: changes in blood cholesterol levels (total cholesterol in mg/dl), blood pressure readings (mmHg), glycosylated haemoglobin A1c level (mm/mol)).

Secondary outcomes

- Cost effectiveness.
- Patient and provider satisfaction with the methods.
- Adverse events (Composite outcome including: CVD mortality and morbidity).
- Response rates to invitations for (lifestyle) assessment or CVD; Patient compliance with treatment.
- Biomarker readings (Composite outcome: includes changes in blood cholesterol levels, blood pressure readings and glycosylated haemoglobin A1c level).
- Cost effectiveness.
- Patient and provider satisfaction with the methods.
- Adverse events (Composite outcome: includes cardiovascular-related mortality (i.e. death due to CHD or stroke), increased cardiovascular-related morbidity (i.e. increased recurrence of a cardiovascular event) and hospitalisation due to a cardiovascular event).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

We searched electronically the following sources for the identification of trials on 18 June 2016:

- CENTRAL (Issue 5 of 12, 2016) on The Cochrane Library,
- MEDLINE (OVID, 1946 to June 2016 week 1),
- EMBASE (OVID, 1980 to 2016 week 24),
- Web of Science Core Collection (Thomson Reuters, 1970 to 13 June 2016),
- DARE, HTA and EED (Issue 2 of 4, 2016) on The Cochrane Library.

We imposed no language limits. The Cochrane precision-maximising RCT filter was used for MEDLINE and terms as suggested as a RCT filter for EMBASE (14).

We also used the following other resources for the identification of trials:

- 'Current Controlled Trials' (www.controlledtrials.com),
- Clinical Trials.gov (www.clinicaltrials.gov),
- WHO ICTRP Portal (apps.who.int/trialsearch).

We tried to identify additional studies by searching the reference lists of included trials, related (systematic) reviews and meta-analyses. Authors of included studies were contacted for further details (if required) and authors and experts in the field were asked for information about unpublished/ongoing trials.

DATA COLLECTION AND DATA EXTRACTION

To determine the studies to be assessed further, three authors (SP, JV and YP) independently scanned the abstract, title or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Where differences in opinion existed, they were resolved by a third party. If resolving disagreement was not possible, the article were added to those 'awaiting assessment' and authors were been contacted for clarification. An adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-charts of study selection is attached (19) see Figures 1 and 2.

For studies that fulfilled inclusion criteria, two authors (SP and PT) independently abstracted relevant population and intervention characteristics using standard data extraction templates with any disagreements resolved by discussion, or if required by a third party. Any relevant missing information on the trial was sought from the original author(s) of the article, if required. Authors and experts in the field were asked for information about unpublished/ongoing trials.

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Two authors assessed each trial and performed assessment of bias independently. Disagreement was resolved by consensus, or with consultation of a third party.

We assessed risk of bias using the Cochrane Collaboration's tool. We used the following criteria:

- Was the allocation sequence adequately generated? Was the allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study? Were incomplete outcome data adequately addressed?

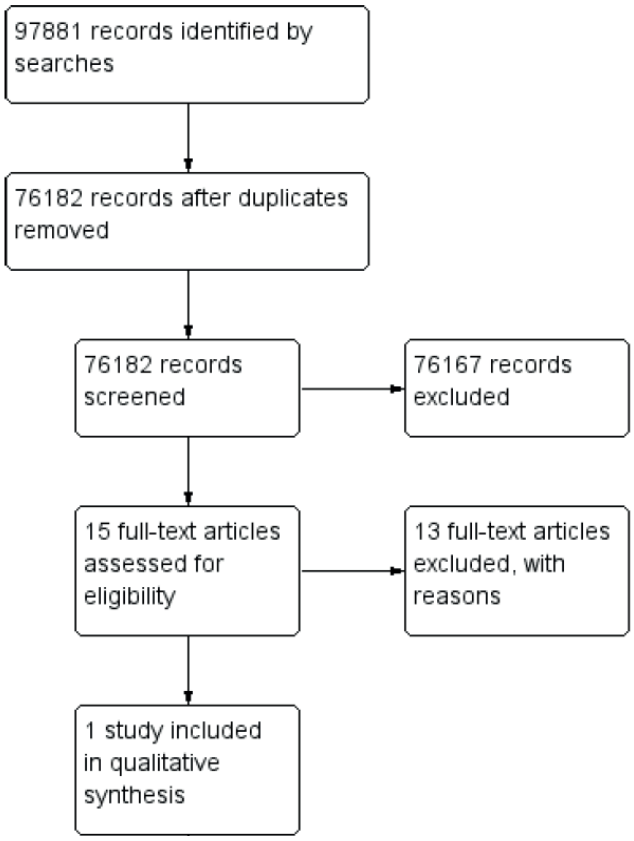

Fig. 1: Flowchart of studies in CVD prevention.

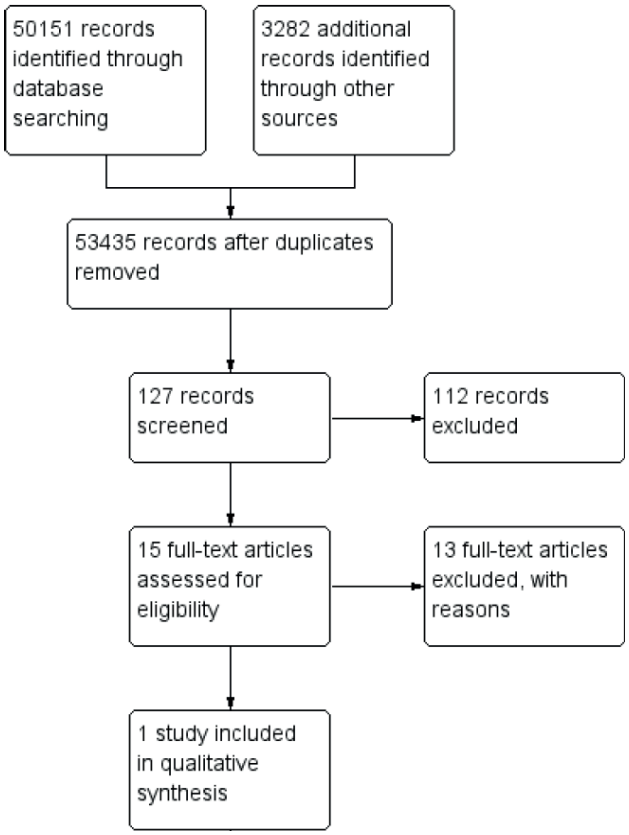

Fig. 2: Flowchart of studies in CVD management.

- Were reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a high risk of bias?

We assessed the risk of bias as high, low or unclear. We used the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (19). Funnel plots were to be used to assess for the potential existence of small study bias. As a number of explanations for the asymmetry of a funnel plot (27) exist, we planned to carefully interpret results (13).

MEASURES OF TREATMENT EFFECT

We collected endpoint scores, as change standard deviations may not be available for many studies. If both endpoint and change scores are available for the same outcomes, only the former was reported in this review. If endpoint scores are not available, but change scores are, we reported the latter in the tables and text of the review. However, for inclusion of a study reporting change score in the meta-analysis, we calculated the endpoint mean from the change score given and assumed that the endpoint standard deviation is equal to the baseline standard deviation. We also took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

There were no missing data in the included studies. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat and per-protocol population was carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and techniques to handle these (for example, last-observation-carried-forward) was critically appraised.

ASSESSMENT OF HETEROGENEITY

The review included two studies one on the prevention of CVD and one on the management of CVD and no assessment of heterogeneity was needed. Results of the studies included were presented in narrative form.

RESULTS

Results were divided into two categories according the main use of CAHTS:

- CVD Prevention,
- CVD Management.

These two categories are reflected in the objectives of the review and the search strategy.

PREVENTION

Results of the search

The search identified 97881 records for screening; 76182 after removing duplicates. The titles of the records were screened by two authors. 127 records were further screened by abstract and 15 were retrieved in full text. One record met the inclusion criteria of the review. Reasons for excluding the abstracts included: participants not having

pre-existing cardiovascular disease, no computer-assisted history taking systems being used as intervention, or the studies were not randomized controlled trials. See Figure 1 for a detailed search strategy.

For included studies see Table 1. One study (43) met our inclusion criteria, the details of which can be found in Characteristics of included studies. For excluded studies see Table 3.

Tab. 1: Characteristics of included studies (CVD prevention).

Author	Reasons for inclusion
Sheridan et al. (2006)	This study was used to test the effectiveness of an individually-tailored, computerized decision aid about CHD on patients' discussions with their doctor and their plans for CHD prevention. Participants were identified from daily clinician schedules and after obtaining clinician's permission, they were approached about the study in the waiting room or in the exam room as they waited for their scheduled visit. 75 adults were enrolled. 41 received decision aid, 34 usual care. After assessing baseline characteristics, all patients in the intervention group were asked to review the computerized decision aid, Heart to Heart. Heart to Heart 1) calculates a patient's global risk of CHD events (e.g. angina, myocardial infarction, and death) in the next 10 years by combining information about their age, sex, blood pressure, total and HDL cholesterol, smoking, diabetes and left ventricular hypertrophy status using a continuous Framingham equation. 2) provides patients with individualized information about their global CHD risk, their personal risk factors, the pros and cons of pertinent CHD risk-reducing therapies (e.g. hypertension medication, cholesterol medication, smoking cessation and aspirin), and the risk reduction achievable after one or more therapeutic interventions 3) encourages patients to choose therapies that are acceptable and feasible for long-term CHD risk reduction.It also provides a summary print-out that can be taken to one's visit with his or her doctor. The patients navigated the decision aid at their own speed. A research assistant was available at all times to answer any questions.

Tab. 1.1: Risk of bias.

Sheridan et al. (2006)		
Type of bias	**Severity of bias**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: We used a computerized random number generator to randomize patients to receive either the Heart to Heart decision aid or a list of their CHD risk factors that they could present to their doctor.
Allocation concealment (selection bias)	Low risk	Quote: Intervention assignments were sealed in security envelopes until after subjects agreed to participate in the study. The research assistant then broke the seal to determine intervention assignment.
Blinding (performance bias and detection bias)	Low risk	Participants were blinded.
Blinding of outcome assessment (detection bias)	High risk	The research team weren't blinded
Incomplete outcome data (attrition bias)	Low risk	Twelve patients (8 in the decision aid group and 4 in the control group) were subsequently determined to be ineligible with those in the decision aid group being slightly more likely to be male and younger. These individuals were excluded from further analyses
Selective reporting (reporting bias)	Low risk	No selective reporting was detected.
Other bias	Low risk	None identified

Effects of interventions in CVD prevention

75 adults were enrolled. 41 patients received the decision aid and 34 received usual care The main effect of the decision aid on decision making was measured in 2 ways: 1) by the proportion of patients who reported they discussed CHD risk with their doctor, and 2) by the proportion of patients that talked with their doctor who reported they had a specific plan for CHD risk reduction at the post-visit survey. Sheridan et al. (2006) measured patient discussions with their doctor through a single question: "Did you and your doctor discuss a plan to lower your chances of having a heart attack?" Sheridan et al. (2006) measured plans for CHD risk reduction through a single question: "At the end of your visit, what did you decide to do, if anything, to lower your chances of heart disease?" Sheridan et al. (2006) considered stated intent to adopt any CHD risk reducing behaviour (i.e. aspirin, lipid lowering medication, antihypertensive medication, smoking cessation medications, dietary change, or exercise) in the next 6 months as sufficient evidence of a plan for CHD risk reduction.

In unadjusted analysis, the decision aid increased the proportion of patients who discussed CHD risk reduction with their doctor from 24% to 40% (absolute difference 16%; 95% CI –4% to +37%). In pre-post testing, the decision aid also appeared to increase the proportion of patients with plans to intervene on their CHD risk through initiating aspirin, lipid lowering medication, antihypertensive medication, smoking cessation medication, dietary change or exercise. The study did not look at the other outcome measures included in our protocol including quality of the data recorded, life-

style modifications, biomarker reading modifications, cost effectiveness, patient and provider satisfaction or adverse events.

MANAGEMENT

Results of the search

The search identified 50151 records from databases and 3282 from other resources, giving a total of 53433 records for screening. The titles of the records were screened by two authors (YP, SP). 127 records were further screened by abstract and 14 were retrieved in full text. One record met the inclusion criteria of the review. Reasons for excluding the abstracts included: participants not having pre-existing cardiovascular disease, no computer-assisted history taking systems being used as intervention, or the studies were not randomized controlled trials. See Figure 2 for more detailed flow of our searches.

For included studies see Table 2. One study, Rogers et al. met the inclusion criteria. Details of the study can be found in Characteristics of included studies. For excluded studies see Table 3.

Tab. 2: Characteristics of included studies (CVD management).

Author	Reasons for inclusion
Rogers et al. (1982)	This study describes the influence of a computerized medical record summary system in three disease areas (hypertension, obesity and renal disease) observed in the course of a controlled, randomized and prospective study of 479 Northwestern University Cardiac, Pulmonary and Renal Clinic (NUCPRC) patients. From 1,200 eligible patients, 484 were randomly selected and assigned to either the experimental or control group. 241 participants were assigned to the experimental group and 238 in the control group. Five participants withdrew from the study before it began. The NUCPRC developed a computerized medical record system (NUCRSS) to provide physicians with concise and current information on patients' problems, to identify omissions in recording of observations and treatment recommendations, to show ordered procedures that were not carried out, to record deficiencies in medical reasoning and, most importantly, to recommend corrective actions according to selected criteria. In the experimental group, patients had available a computer printout of a current NUCRSS summary in addition to the traditional medical record, while the control group had available only the handwritten, traditional medical record. Hypertension: examination of the renal function occurred more frequently during both years of the study I n the experimental group (120 times in experimental group and 93 times in control group). There was little difference in distributions across conditions for either the fundusopic examination (14 vs 9) or the intravenous pyelogram (78 vs 59). Obesity: failure to give or review a diet at any time during the two-year study period clearly occurred less often among experimental patients (number of diets given or reviewed: 23 in experimental group and 16 in control group). Renal disease: there were fewer experimental patients who had not had a urine analysis performed either year, while more experimental patients had tests performed both years (30 vs 14).

Tab. 2.1: Risk of bias.

Type of bias – Rogers et al. (1982)	Severity of bias	Author
Random sequence generation (selection bias)	High risk	Rogers et al. (1982) stated the randomization process was performed as follows: From 1,200 eligible patients, 484 were selected and assigned to either an experimental or control group. It is not clear whether the participants were randomly selected or assigned to a group.
Allocation concealment (selection bias)	High risk	As above
Blinding (performance bias and detection bias)	Unclear risk	In the experimental group, patients had a computer printout of a current North wester University computerized medical record system summary (NUCRSS) in addition to the traditional medical record, while the control group had only the handwritten, traditional medical record. Physicians participating in the study were randomly divided into three groups: 1) those that were only to see patients with automated records available; 2) those who were to see patients without automated records; and 3) those whose patient load was approximately half with and half without automated records. It would therefore not have been possible to blind participants or physicians to their allocation. Blind retrospective chart reviews were done one and two years after the entry of patients into the study for both experimental and control patients by trained personnel using a standardised evaluation form.
Incomplete outcome data (attrition bias)	Unclear risk	Rogers et al. (1982) reported the number and percentage of patients who died by the end of the two-year study period or were transferred to another clinic, moved or left for unknown reasons. Differential dropout rates across conditions due to death or other reasons were not presented.
Selective reporting (reporting bias)	Low risk	None identified
Other bias	Low risk	None identified

EFFECTS OF INTERVENTIONS IN CVD MANAGEMENT

The effects of the interventions in the Rogers et al. (1982) study were measured according to the performance of selected annual medical tests and procedures that were considered to be essential for the care of patients with hypertension, obesity and renal disease. These were blood tests for renal function, electrolytes, fundoscopy and intravenous pyelogram for hypertension. Urine analysis and culture was also checked for the renal patients. Obese patients were given diet information or had their diet reviewed. The details of the diet were not reported.

Tab. 3: Characteristics of excluded studies.

Author	Reason for exclusion
Baer et al. (2012)	Full text of this study was not available, even after contacting the authors.
Bulpitt et al. (1976)	Investigation results not often present in the notes.
Davis et al. (2010)	Experimental group not computer-assisted history-taking.
Gill et al. (2009)	Electronic health records used in both groups.
Khambatta et al. (2011)	Not RCT.
Lowensteyn et al. (1988)	Control group only received cardiovascular risk profile if the patient was clinically re-evaluated during a 3 month follow-up visit.
Ruffin et al. (2011)	Familial risk assessed only.
Sequist et al. (2011)	Electronic health records used in both groups.
Sequist et al. (2012)	The aim is to identify subsequent actions following a risk alert. This outcome is not included in our protocol.
Sheridan et al. (2006)	Study participants did not have a history of cardiovascular disease.
Sheridan et al. (2011)	Study participants did not have a history of cardiovascular disease.
Van Wyck et al. (2003)	Abstract prospective, full article not located.
Wakefield et al. (2012)	Study does not compare electronically gathered data to data gathered in oral and/or written form.

PRIMARY OUTCOMES FOR PREVENTION AND MANAGEMENT

Quality of data recorded (Composite outcome: includes error rates, completeness, accuracy, reliability) and lifestyle modifications (Composite outcome: includes changes in tobacco consumption, weight, dietary intake and physical activity levels): the results of the study show that generally the patients in the experimental group underwent more laboratory procedures, and/or were given (or had reviewed), more diets than the control group. There was a statistically significant difference in the number of hypertensive patients who had their renal function checked, the number of diets given or reviewed for obese patients, and the number of urine cultures checked for patients with renal disease. These are all tests that are considered essential for high quality, routine care of patients with cardiovascular disease. The results therefore suggest that computer-assisted methods of history-taking are more effective for the management of cardiovascular disease.

The paper does not comment on adverse effects but does describe mortality rates. About a third of patients died of hypertension (28% in the experimental group and 33% in the control group). 10% died in the renal group (10% of both the experimental and control group). 8% died in the obesity group (1% of the experimental group and 7% of the control group).

RISK OF BIAS IN INCLUDED STUDIES (TABLE 2.1)

Overall the risk of bias for Sheridan et al. was low. The risk of bias for Rogers et al. (1982) was high.

DISCUSSION

Discussion is divided into two categories according to the aims and initial searches. The two categories are:

- CAHTS for CVD Prevention,
- CAHTS for CVD Management.

CAHTS FOR CVD PREVENTION

The comprehensive search strategy for studies on the use of CAHTS for CVD prevention yielded 97881 results, of which one met our inclusion criteria. A randomized trial was carried out to test the effectiveness of an individually-tailored, computerized decision aid about CHD on patients' discussions with their doctor and their plans for CHD prevention. A computerized random number generator was used to randomize patients to receive the intervention, the computerised Heart to Heart decision aid, or the control which was a list of their chronic heart disease (CHD) risk factors that they could present to their doctor. This list included qualitative identification of the risk factors and, where appropriate, a quantitative value for the following risk factors: blood pressure, total and HDL cholesterol, smoking, diabetes, and left ventricular hypertrophy (LVH) status. The computerized decision aid allows computer-assisted history-taking of patients' CVD risk factors. For more information on how it uses this information see Table 1. 75 adults were enrolled. 41 patients received the decision aid and 34 received usual care. The main effect of the decision aid on decision making was measured in 2 ways: 1) by the proportion of patients who reported they

discussed CHD risk with their doctor, and 2) by the proportion of patients that talked with their doctor who reported they had a specific plan for CHD risk reduction at the post-visit survey. Sheridan et al. (2006) measured patient discussions with their doctor through a single question: "Did you and your doctor discuss a plan to lower your chances of having a heart attack?" Similarly, Sheridan et al. (2006) measured plans for CHD risk reduction through a single question: "At the end of your visit, what did you decide to do, if anything, to lower your chances of heart disease?" Sheridan et al. (2006) considered stated intent to adopt any CHD risk reducing behaviour (i.e. aspirin, lipid lowering medication, antihypertensive medication, smoking cessation medications, dietary change, or exercise) in the next 6 months as sufficient evidence of a plan for CHD risk reduction. In unadjusted analysis, the decision aid increased the proportion of patients who discussed CHD risk reduction with their doctor from 24% to 40% (absolute difference 16%; 95% CI −4% to +37%). In pre-post testing, the decision aid also appeared to increase the proportion of patients with plans to intervene on their CHD risk through initiating aspirin, lipid lowering medication, antihypertensive medication, smoking cessation medication, dietary change or exercise. Overall assessment of risk of bias was low. There are no other reviews on the use of CAHTS for the prevention of cardiovascular disease. Other studies (43, 53, 41, 32, 54, 7) assessed the use of CAHTS on cardiovascular disease prevention and management, but these either did not compare oral to written history taking processes or were conducted in participants who did have pre-existing cardiovascular disease. In agreement with our findings they generally found that computer-assisted methods improved the prevention or management of patients with cardiovascular disease or with risk factors for cardiovascular disease.

CAHTS FOR CVD MANAGEMENT

The comprehensive search strategy for studies on the use of CAHTS for CVD management yielded 50151 results, of which one met our inclusion criteria (39) This study is a randomized, controlled prospective study looking at the influence of a computerized medical record summary system in three disease areas (hypertension, obesity and renal disease) in 479 Northwestern University Clinic patients. Patients in the experimental group had computerised record summaries whilst patients in the control group had only a hard copy medical record. They were compared on several medical tests and procedures whose yearly occurrence was considered good medical practice for this patient population. These were blood tests for renal function, electrolytes, fundoscopy and intravenous pyelogram for hypertension. Urine analysis and culture was also checked for the renal patients. Obese patients were given diet information or had their diet reviewed. The details of the diet were not reported. For more detailed information please see Table 2. The results of the study show that generally the patients in the experimental group underwent more laboratory procedures, and/or were given (or had reviewed), more diets than the control group. These laboratory procedures give the biomarker readings which are stated in our protocol as appropriate outcome measures for our review.

Rogers et al. (1982) also reports that the traditional non-computerised records used in the clinics contained an average of 1.5 pounds of notes, laboratory test outcomes, diagnoses and other information not entered over long periods of time by the physicians. This may have affected continuity of care, especially as patients were not necessarily seen by the same physician from visit to visit. The same authors further noted that the computerised information system condensed the records to items that were current and relevant, providing physicians with warnings and reminders about good medical practices. These comments regarding the medical records provide evidence for quality of data, a further outcome measure stated in our protocol.

Traditionally a patient's history is taken by oral-and-written methods; however, it can also be taken using computers. Although computer-assisted history taking systems (CAHTS) have been available (in various forms) since the 1960s (2), wide and systematic adoption in routine delivery of healthcare remains variable. CAHTS, such as a web-based questionnaire or interactive touch screen monitors, are tools used to aid clinicians in gathering information from patients. They can be used by healthcare professionals, or directly by patients, as in the case of pre- or post-consultation interviews (34, 38, 52). CAHTS can be used remotely, for example via the Internet, telephone or mobile phone messaging or on-site. Bowling (2005) describes that the various CAHTS typologies depend on three interrelated factors: a) the information technology used to collect the information (e.g. personal computer, personal digital assistant, Internet, telephone); b) the mode of administration (e.g. administered by an interviewer or self-administered); c) the channel of presentation (e.g. auditory, oral or visual). The CAHTS typologies can be classified as computer-assisted self-administering interviewing and audio computer-assisted self-administered interviewing, computer-assisted face-to-face interviewing, computer-assisted telephone interviewing, interactive voice response telephone interviewing and Internet-based computer-assisted history taking. Given the social and psychological value ascribed to lifestyle choices, asking a person about these in general practice makes responses vulnerable to social desirability bias (a tendency to behave in a way that is believed to be socially acceptable and desirable). Computer interviewing is effective for obtaining personal information that many people find difficult to discuss face-to-face as the systems can collect patient data without the need for a face-to-face interviewer (46); CAHTS may therefore help to reduce the social desirability bias in patient-reporting of harmful lifestyle choices or behaviors. Computers cannot however detect non-verbal communication, which may be important or relevant for a patient's treatment plans that could be identified in a face-to-face consultation (34).

There are no other reviews on the use of CAHTS for the management of cardiovascular disease. Other studies (17, 43, 53, 41, 54, 7, 55) assessed the use of CAHTS on cardiovascular disease prevention and management, but these either did not compare oral to written history taking

processes or were conducted in participants who did not have pre-existing cardiovascular disease. In line with our review they generally commented that computer-assisted methods improved the management of patients with cardiovascular disease or with risk factors for cardiovascular disease.

Bulpitt et al. (1976) found that in three hypertension clinics, certain symptoms and risk factors for cardiovascular disease were recognised more often when computer-held records were used instead of standard hospital notes. Davis et al. (2010) found a reduction in glycated Haemoglobin in diabetic patients when a remote comprehensive diabetes self-management education intervention was used. LDL cholesterol was also reduced when compared with usual care. Davis et al. (2010) also cites Hivert et al. (2009) who tested the effects of a web-based decision support tool, the diabetes Disease Management Application (DMA), developed to improve evidence-based management of type 2 diabetes. The number of HbA(1c) tests obtained per year increased significantly in the intervention group compared with the control group, as did the number of LDL cholesterol tests and the proportions of patients undergoing at least one foot examination per year. Levels of HbA(1c) decreased by 0.2 in the intervention group and increased by 0.1 in the control group, proportions of patients with LDL cholesterol levels <130 mg/dl increased by 20.3% in the intervention group and 10.5% in the control group. These results suggest that web-based patient-specific decision support has the potential to improve the parameters of diabetes care, which is relevant to our research question due to their use of computer-assisted decision support tools and the importance of diabetes as a risk factor for cardiovascular disease. If the diabetes can be improved with computer-assisted history taking this consequently impacts on the prevention of cardiovascular disease.

Gill et al. (2009) found improved outcomes in patients at high-risk of cardiovascular disease when an electronic form containing prompts regarding sub optimal care was integrated into the electronic medical record. The 3 main outcome variables were defined accordingly: the proportion of patients tested adequately for hyperlipidaemia, the proportion of patients whose most recent low-density lipoprotein cholesterol (LDL-C) was at goal, and the proportion of patients at high risk of cardiovascular disease with an LDL-C > 130 who were prescribed lipid-lowering medications. The study showed improvements in the quality of lipid management after implementing an electronic disease management intervention in primary care. Lowensteyn et al. (1988) found improved identification of patients at high-risk of cardiovascular disease when computer-generated risk profiles were used. Their use was also associated with a significantly greater improvement in serum lipid profiles and overall coronary risks. Ruffin et al. (2011) found that a self-administered web-based tool that assesses familial risk for 6 common diseases including cardiovascular disease and provides personalised risk-tailored messages, increased self-reporting of physical activity and healthy eating. This is consistent with the findings of the current study which found that experimental patients had their diets reviewed more frequently and evidenced greater weight loss on average than control patients. Evidence of improvement in weight loss is relevant to our research question due to the importance of obesity as a risk factor for cardiovascular disease. The use of computer-assisted tools to increase weight loss may consequently help to improve cardiovascular disease prevention and management. Rogers et al. (1982) also found that the traditional record used in the clinics contained on average 1.5 pounds of notes, laboratory test outcomes, diagnoses and other information entered over long periods of time by different physicians. The computerized system, in addition to condensing the medical information to items that were current, legible and relevant, also provided physicians with warnings and reminders concerning good medical practices.

Our findings are consistent with other reviews on the use of computer-assisted history taking systems (CAHTS) for diabetes such as Pappas et al. (2011) which found that CAHTS can save professionals' time, improve delivery of care to those with special needs and also facilitate the collection of information, especially potentially sensitive information (e.g. sexual history, alcohol consumption). The findings are consistent with another systematic review, Wei et al. (2011) that found computer-assisted diet history taking to be as accurate as the oral-and-written method. However, this systematic review only included one study so we are unable to make robust conclusions.

LIMITATIONS

Biases in the review process were prevented by involving three reviewers in the data extraction and assessment of bias processes. All studies that met the initial inclusion criteria and were not in English were reviewed by colleagues who were either native speakers of the respective languages or bilingual. Although CAHTS can facilitate the history taking in several languages, it is possible that some patients speak none of the languages offered by the system.

CONCLUSIONS

In this review of the literature, we aimed to assess the effect of computer-assisted versus oral-and written history taking on the quality of collected information for the prevention and management of CVD. Also, to assess the effect of computer-assisted versus oral-and written history taking on the prevention and management of CVD. We searched all major databases. We identified two studies. The limited evidence in this review shows that an individually-tailored computerized decision aid about cardiovascular disease prevention appears to increase the proportion of patients who discuss cardiovascular disease prevention with their doctors and the proportion of patients who have a specific plan for CHD risk reduction. These findings were corroborated by within group differences that showed an increase in the perception that cardiovascular disease requires a personal decision and a specific plan for risk reduction. This might be clinical-

ly relevant but further research evidence is needed. We tentatively conclude that CAHTS can provide individually-tailored information about CVD prevention. However, further primary studies are needed to confirm these findings. There is a need to develop an evidence base to support the effective development and use of CAHTS in this area of practice.

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S100A4 Protein in Inflammatory Bowel Disease: Results of a Single Centre Prospective Study

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ABSTRACT

Introduction: The aim of our study was to assess association of serum S100A4 protein with ulcerative colitis (UC) and Crohn's disease (CD).
Methods: Study included 118 subjects: 93 patients with CD, 16 with UC and 9 controls. In CD group, 20/93 patients had B1 phenotype, 19/93 B2, 20/93 B3 and 34/93 B2 + B3. L1 involvement was present in 15/93, L2 in 14/93 and L3 in 64/93 patients. Serum S100A4 concentration was investigated in peripheral venous blood samples by means of ELISA.
Results: Serum S100A4 was significantly higher in UC (158.6 ± 56.2 ng/mL), $p = 0.019$ and in CD (154.4 ± 52.1 ng/mL), $p = 0.007$ compared to controls (104.8 ± 40.5 ng/mL). No difference in S100A4 was revealed between UC and CD, $p > 0.05$. Serum S100A4 in each CD subgroup (according to behaviour) was significantly higher compared to controls, $p < 0.05$. Serum S100A4 was significantly higher in L2 (144.6 ± 44.2 ng/mL), $p = 0.041$ and in L3 (163.0 ± 52.8 ng/mL), $p = 0.002$ compared to controls and in L3 compared to L1 (126.9 ± 47.6 ng/mL), $p = 0.017$.
Conclusion: Association of serum S100A4 protein with UC and CD was confirmed. In CD, disease behaviour did not influence serum concentration of S100A4 protein. In CD, higher levels of serum S100A4 were observed in patients with ileo-colonic and colonic involvement compared to those with isolated small bowel involvement.

KEYWORDS

S100A4 protein; inflammatory bowel disease; ulcerative colitis; Crohn's disease

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INTRODUCTION

Inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD) have become a global disease. Molodecky et al. reported in their recent study, that incidence and prevalence of IBD have been increasing worldwide. The highest prevalence of IBD has been documented in Europe and Canada (1).

Despite all the progress in contemporary diagnostics in medicine, there is no serum marker, which would be specific for IBD. Serum markers of inflammation – decreased thrombocyte volume and/or elevated thrombocyte count, white blood cell count, erythrocyte sedimentation rate and C-reactive protein – help to assess activity of IBD, mainly (2–7). Whichever antibody or combination of antibodies associated with IBD, including serum ASCA (anti-*Sacharomyces cerevisiae* antibodies), ABBA (anti-brush border antibodies), anti-I2 (antibodies to DNA fragments of *Pseudomonas fluorescens*), Anti-CBir1 (antibodies to CBir1 flagellin), anti-GP2 (antibodies to glycoprotein 2), anti-OmpC (anti-outer membrane protein C antibodies), pANCA (perinuclear anti-neutrophil cytoplasmic antibody), different levels of serum IgG1 and IgG2, ALCA (anti-laminaribioside carbohydrate antibodies), ACCA (anti-chitobioside carbohydrate antibodies) are present (8–15), their role to establish the definitive diagnosis of IBD/UC/CD is still supportive only.

The family of S100 proteins represents a total of at least 25 small calcium binding proteins. S100 proteins have a broad range of functions – they play an important role in the regulation of cell proliferation, differentiation, apoptosis, energy metabolism, cellular signalling, and calcium homeostasis (16). Involvement of S100 proteins in the pathogenesis of IBD has been clearly documented and the role of individual S100 proteins as biomarkers for CD and UC has been validated in multiple studies (17–23).

Calprotectin, a heterocomplex of S100A8/9 proteins, plays an important role in the regulation of different inflammatory processes and nowadays, faecal calprotectin is used for assessment of IBD activity on routine basis (17, 24).

S100A4 (metastatin-1, calvasculin) is localized in the nucleus, cytoplasm, and extracellular space. It is strongly associated with metastatic tumour progression (25).

Boye et al. emphasized that the nuclear expression (not the cytoplasmic one) of S100A4 is a novel prognostic marker for colorectal cancer (26) and further studies showed that S100A4 is not a biomarker only, but mediates the metastatic process itself, too (27).

Recent research has revealed that the role of S100A4 is more complex, including profibrotic effect e.g. in the myocardium, liver and intestine (28–30). Significant upregulation of S100A4 was observed in certain chronic inflammatory conditions, especially in patients with rheumatoid arthritis. It was shown, that increased secretion of TNF-α, IL-1β and IL-6 was mediated by S100A4 (31). The studies have demonstrated, that Toll-like receptor 4 (TLR-4), which plays a significant role in IBD, was involved in these pro-inflammatory S100A4 mediated processes (32, 33).

Fibroblasts represent the key cell type in the pathogenesis of fibrostenosing/stricturing CD. Cunningham et al. investigated S100A4 in ex-vivo culture of resected ileum in patients suffering from fibrostenosing CD. The explant culture of tissue originating from the stricture showed a significant overexpression of S100A4 (30).

We are fully aware, that faecal biomarkers, including calprotectin and S100A12, might have advantage over the serum biomarkers for their anticipated higher sensitivity (being produced by the inflamed mucosa into the intestinal lumen) and higher specificity (as serum biomarkers can be elevated due to non-gastrointestinal disorders) (17). Nevertheless, not a very rare preference of serum sampling to the faecal one by patients with IBD provoked us to investigate S100A4 protein in the serum.

To our best knowledge, there are no studies on S100A4 in different clinical IBD phenotypes in the literature.

The aim of our prospective study was to investigate serum S100A4 protein in patients with IBD and to determine possible association of increased serum S100A4 with complicated forms of CD.

METHODS

SUBJECTS

A total of 118 subjects were enrolled in the prospective study between 2009 and 2016: 93 patients with CD (44 men, 49 women, aged 22–79, mean 44 ± 14), 16 patients with UC (8 men, 8 women, aged 20–74, mean 39 ± 15) and 9 healthy controls (2 men, 7 women, aged 23–74, mean 52 ± 17). Control group consisted of individuals with normal findings on colonoscopy, who had negative history of IBD and/or colorectal neoplasia. A recent change in bowel habit and symptoms compatible with irritable bowel syndrome were the indications for colonoscopy in that individuals. No patient in control group had any serious comorbidities in relation to the serum S100A4 protein (including rheumatic disorders).

CD group was divided according to the Montreal classification (34) and descriptive statistics is provided in Table 1.

The duration of UC was 3–18 years, mean 10 ± 4, the duration of CD was 1–39 years, mean 15 ± 9. At the time of sampling, three patients with CD were without any treatment, 46 patients were on 5-aminosalicylates (5-ASA) and 44 were treated with immunosuppressive therapy (corticosteroids, azathioprine, anti-TNF, cyclosporine). A total of 18% (17/93) were treated with anti-TNF agents, 4/17 with adalimumab and 13/17 with infliximab. A total of six CD patients were treated with antibiotics (ciprofloxacin and/or metronidazole) including one patient in group with 5-ASA and five CD patients with concomitant immunosuppressive therapy.

Within the UC group, all of the enrolled patients had 5-ASA; 3 patients were also treated with azathioprine. No patient from UC group received anti-TNF therapy.

SERUM CONCENTRATION OF S100A4 PROTEIN: SAMPLE COLLECTION AND MEASUREMENT

Venous blood samples (total amount of 6 mL) were obtained before a standard colonoscopy at the Endoscopy

Tab. 1: The main characteristics of CD group.

Behaviour	Subjects Number, (%)	Men/Women	Age	
			Range	Mean
B1	20/93 (22%)	4/16	22–64	40 ± 14
B2	19/93 (20%)	11/8	23–79	48 ± 15
B3	20/93 (21%)	13/7	24–59	39 ± 12
B2 + B3	34/93 (37%)	16/18	24–78	47 ± 14
perianal	27/93 (29%)	13/14	24–69	43 ± 14
Location				
L1	15/93 (16%)	9/6	22–63	41 ± 13
L2	14/93 (15%)	4/10	22–64	45 ± 12
L3	64/93 (69%)	31/33	22–79	44 ± 15

Unit, 2nd Department of Internal Medicine-Gastroenterology. Samples were transferred immediately to the Institute of Clinical Biochemistry and Diagnostics at University Hospital Hradec Králové. Blood centrifugation followed and sera had been stored at –80 °C until the investigation was performed in December 2016. Serum concentration of S100A4 protein was investigated by means of Human Protein S100-A4 ELISA kit, the quantitative sandwich enzyme immunoassay technique (purchased from MyBio Source, San Diego, California, USA).

ETHICAL ISSUES

All subjects included in the study were given the necessary information and provided informed consent via a signed form. The project was approved by the Joint Ethical Committee (Charles University, Faculty of Medicine in Hradec Králové, University Hospital Hradec Králové). For all obtained data, all personal identification information was removed in compliance with the Czech laws for protection of confidentiality.

STATISTICAL ANALYSIS

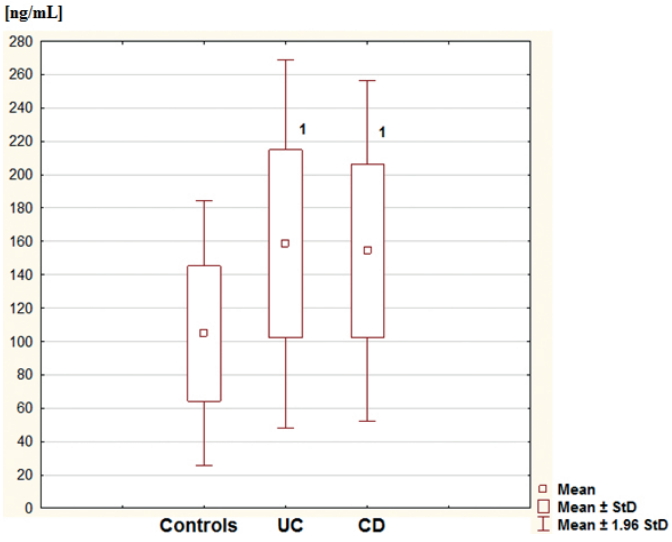
Obtained data were tested statistically by means of descriptive statistic and non-paired t-test (normal distribution of data was confirmed) using STATISTICA software, version 13, 2013, Tulsa, OK, USA.

RESULTS

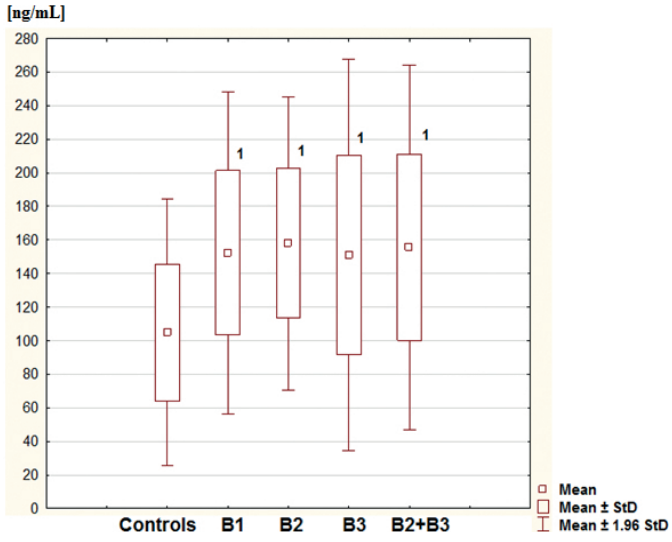
Serum S100A4 values were significantly higher in UC compared to controls, p = 0.019. Serum S100A4 were significantly higher in CD compared to controls, p = 0.007. No difference in S100A4 serum levels was revealed between UC and CD group, p = 0.771. See Graph 1.

In CD group, serum S100A4 was significantly higher in patients with all CD phenotypes compared to controls, p < 0.05. No difference in S100A4 was documented between particular subgroups of CD (divided according to behaviour of CD), p > 0.05. See Graph 2.

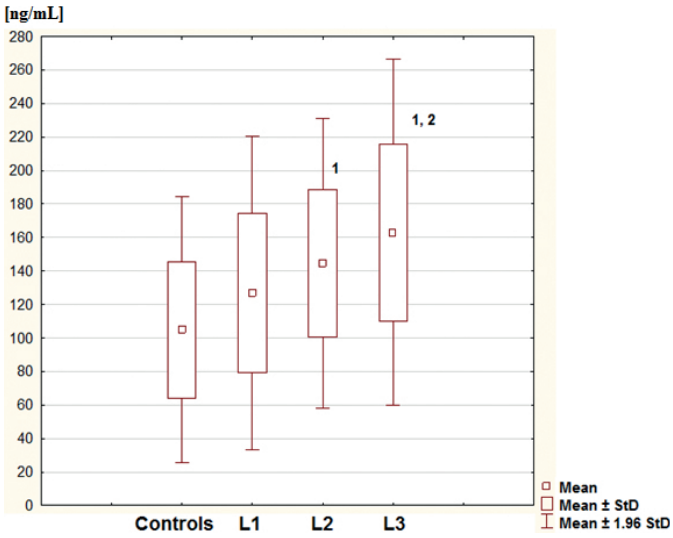
According to disease localisation in CD group, a statistically significant difference in S100A4 was revealed



Graph 1: Comparison of serum concentration of S100A4 protein in controls, UC and CD patients.
1: significant difference compared to controls, p < 0.05.



Graph 2: Comparison of serum concentrations of S100A4 protein in CD subgroups (divided according to the disease behaviour).
B1 = nonstricturing-nonpenetrating, B2 = stricturing,
B3 = penetrating, B2 + B3 = stricturing and penetrating form of CD.
1: significant difference compared to controls, p < 0.05.



Graph 3: Comparison of serum S100A4 protein in controls and CD subgroups (divided according to the disease localization).
L1 = isolated small bowel involvement, L2 = isolated colonic involvement, L3 = ileo-colonic involvement.
1: significant difference compared to controls, $p < 0.05$.
2: significant difference compared to L1, $p < 0.05$.

between L2 subgroup compared to controls, $p = 0.041$ and between L3 compared to controls, $p = 0.002$. Significant difference in S100A4 was revealed between L1 and L3, $p = 0.017$. See Graph 3.

CD patients with (27/93; 29 %) and without perianal involvement (66/93; 71 %) had significantly higher serum S100A4 (mean 163.1 ± 60.6 ng/mL; mean 150.8 ± 48.3 ng/mL, respectively) compared to controls, $p = 0.002$. The difference in serum S100A4 between CD with and without perianal involvement was not statistically significant, $p > 0.05$.

All CD patients, regardless if treated with anti-TNF agents, had significantly higher serum concentration of S100A4 compared to controls: CD group with anti-TNF: mean 154.7 ± 65.5 ng/mL, $p = 0.049$; CD group without anti-TNF: mean 154.3 ± 49.2 ng/mL, $p = 0.005$. There was no significant difference in serum S100A4 between CD patients with and without anti-TNF medication, $p > 0.05$.

DISCUSSION

In our study, serum S100A4 levels were significantly elevated in patients with ulcerative colitis and in patients with Crohn's disease compared to controls. We are convinced, that S100A4 is not a biomarker of IBD only, but it also plays a crucial role in the development of inflammatory process itself, presumably through the activation of TLR receptors and NF-κβ signalling pathway, too. In patients with rheumatoid arthritis, high levels of S100A4 were associated with a poor clinical response to infliximab and a high rate of anti-infliximab antibodies (35). Based on these data, similar situation could be expected in IBD patients and therefore a study evaluating S100A4 before the patients are started on anti-TNF therapy is being planned in our setting. No difference in serum S100A4 was confirmed between CD patients with and without anti-TNF in our study, however no firm conclusions can be drawn from this, as no one has studied the impact of anti-TNF therapy on serum S100A4 so far. S100A4 protein, known as calvasculin or metastatin-1 (16), was isolated by Ebralidze in 1989 and was considered to be involved in the metastatic tumour cell phenotype (36). A recent metaanalysis carried out by Liu et al. was in agreement: they reported that S100A4 over-expression correlates with tumour progression and poor prognosis of patients with colorectal carcinoma (37).

Recent studies have documented, that S100A4 does not play a role in metastatic cancer only, but it is also involved in inflammatory processes (38). Increased expression of calvasculin was documented in inflamed muscle tissue in patients with idiopathic inflammatory myopathies, where S100A4 may stimulate mononuclear cells to increase synthesis of pro-inflammatory cytokines (39). Significant up-regulation of S100A4 was also observed in patients with rheumatoid arthritis: a study performed by Cerezo et al. documented that calvasculin induces inflammatory response (up-regulated production of TNF (tumour necrosis factor)-α, IL (interleukin)-1β and IL-6) of mononuclear cells via the TLR-4 (toll-like receptor) and by the activation of NF-κB signalling pathway (31). Aberrant TLR signalling is known to contribute to intestinal inflammatory processes in IBD and associated carcinoma (32, 33). NF-κβ signalling cascade has also been shown to be involved in the development of colitis associated carcinoma (40).

Cunningham et al. found increased expression of S100A4 in fibroblasts and immune cells in the resected ileum in patients with stricturing CD. They also reported that the over-expression of S100A4 was induced by TGF-β1 (transforming growth factor) (30). Therefore we assumed, that patients with stricturing phenotype of CD will have higher serum S100A4 compared to those with a non-stricturing CD behaviour. Nevertheless, our data have shown that patients with all phenotypes of CD had significantly elevated serum S100A4 compared to controls and no significant difference in serum S100A4 was observed between stricturing and non-stricturing CD phenotypes. This might be explained by the fact, that over-expression of S100A4 in fibrotic processes is observed in tissue specific manner reflecting the local situation in the damaged tissue. We hypothesize therefore, that elevation of serum S100A4 protein (found in both, patients with UC and CD), mirrors rather inflammatory properties of calvasculin and its involvement in inflammatory processes in IBD.

Role of S100A4 in fibrotic processes has been investigated recently: Tamaki et al. studied effect of S100A4 on cardiac fibrosis and documented, that S100A4 knockout mice showed reduced interstitial fibrosis, decreased number of myofibroblasts, suppressed expressions of collagen and profibrotic cytokines in the left ventricle. The authors assume, that the S100A4 induces cardiac fibrosis through the modulation of p53 (28). Effect of S100A4 in the ischaemic myocardium seems to be different – protective and regenerative mainly: calvasculin decreased apoptosis of cardiac myocytes via the AKT signalling pathway (41) or via the ERK pathway (42).

We found the presence of highest S100A4 levels in patients with ileo-colonic and colonic forms of CD very interesting. Based on the literature, there is no definitive

explanation for this. Nevertheless, (1) reported activation of NF-κβ signalling cascade by S100A4 (31), (2) suggestion that the NF-κβ signalling cascade may be the central mediator of gastrointestinal inflammation in IBD and malignancies (40), (3) known properties of metastatin – being a mediator of metastatic processes (27), (4) and known association of colorectal carcinoma with IBD (43) are compatible with our observation of higher levels of serum S100A4 in IBD patients with colonic involvement.

We are aware of the possible limits of our current study. On the basis of the available literature, where S100A4 was investigated either in the serum (51 studies; two of them in a relation to a gastroenterology disorder – liver fibrosis and cirrhosis (44, 45)) or in plasma samples (26 studies; two of them were accomplished in gastric and colorectal cancer (46, 47)), we decided to investigate serum S100A4. All individuals enrolled into our study including all healthy controls and all IBD patients were investigated in the same manner. Therefore we assume, that our results are valuable and plausible despite we do not have any comparison between plasma and serum concentrations in our patients. Further, we did not investigate mRNA for S100A4 tissue expression (from the affected areas), therefore it was not possible to correlate it with the serum S100A4. The reasons why we did not investigate the tissue samples were two: a) middle part of the small intestine may not be easily accessible for a routine endoscopy, b) resected specimens might not reflect situation in the whole intestine.

We hypothesize, that serum S100A4 can help to distinguish between IBD and non-IBD population and it possibly might serve as a phenotype marker of IBD (colonic involvement), however further studies are needed to follow in the near future.

CONCLUSIONS

Association of serum S100A4 with inflammatory bowel disease was confirmed.

No difference in serum S100A4 was observed between particular phenotypes of Crohn's disease (CD) including stricturing and non-stricturing forms of CD.

In CD, serum S100A4 was higher in patients with colonic and ileo-colonic involvement compared to patients with isolated small bowel involvement.

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Comparative Evaluation of Effect of Nano-hydroxyapatite and 8% Arginine Containing Toothpastes in Managing Dentin Hypersensitivity: Double Blind Randomized Clinical Trial

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ABSTRACT

Purpose: This double blind randomized clinical trial was conducted with the purpose of evaluating the effects of Nano-hydroxyapatite toothpaste as compared to 8% Arginine containing toothpaste in the management of Dentin hypersensitivity (DH).

Method and materials: Patients (30 in each group) suffering from DH and eliciting a VAS score higher than 2 in air blast and tactile test were randomly allocated (block randomization) into either a group 1 (arginine toothpaste) or group 2 (nHA toothpaste). The primary outcome evaluated was the reduction of DH as measured by the electrical stimulus reading on the digital pulp tester. Current required for eliciting a VAS score of 2 was recorded before application of dentifrice. 1 cm of toothpaste was then expressed on the tooth surface for two minutes in each group and rinsed off. The electrical stimulus required to elicit a VAS score of 2 was recorded after 5 minutes, 1 week and 4 weeks.

Results: The desensitizing paste containing arginine provided a statistically significant reduction in DH and so did the paste containing nHA. Mean increase in amperage value (reduction in DH) was higher for nHA based than the arginine containing dentifrice. This difference was not statistically significant showing that both toothpastes are equally effective.

Conclusions: The findings of the present study encourage the use of Nano-hydroxyapatite and arginine containing dentifrice as an effective desensitizing agent providing relief from symptoms 5 minutes after application and after 1 and 4 weeks.

KEYWORDS

arginine; Dentin hypersensitivity; Nano-hydroxyapatite

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INTRODUCTION

Dentin hypersensitivity (DH) is a common problem in clinical practice and is defined as a short, sharp pain arising from exposed dentin as a result of various stimuli, such as heat, cold, chemical or osmotic, that cannot be ascribed to any other form of dental defect or pathology (1). The condition has a predilection for individuals in their third and fourth decades of life, canines and premolars are usually affected. Brannstrom's hydrodynamic theory is the most accepted explanation for this condition (2, 3). An increase in life expectancy of the population has resulted in a concomitant rise in the prevalence of DH. The disorder can impede adequate maintenance of oral hygiene, thereby contributing to accumulation of dental plaque, caries, gingivitis and periodontal disease (4). DH hence needs to be addressed in order to provide patients with better oral comfort and quality of life.

To date, no gold standard exists for the treatment of DH. The primary approaches used in its management are tubular occlusion and nerve desensitization. The symptoms often reappear because of toothbrush abrasion, acid challenges in the mouth or degradation of the coating material. There is a need to develop desensitizing agents that provide instant and sustained relief from DH symptoms and is economically viable.

Kleinberg et al. (5) in 2002 demonstrated a saliva-based dentifrice containing arginine, bicarbonate and calcium carbonate to form a solid plug, sealing the patent dentinal tubules and limiting fluid movement. The dentifrice provided a statistically significant reduction in DH immediately after a single professional application, which sustained over a period of 28 days (5).

Hydroxyapatite (HA) is the major inorganic constituent of mineralized biological tissues. Orsini et al. (6) reported nHA containing dentifrice to significantly reduce DH after 4 and 8 weeks, supporting its utility in clinical practice.

No study has yet been published comparing the effect of arginine and nHA containing dentifrices. This double blind randomized clinical trial was carried out to identify the more clinically effective dentifrice in the management of DH – immediately, at 1st week and 4th week of use. The null hypothesis generated was that there is no difference in clinical efficacy of nHA toothpaste as compared to arginine containing toothpaste in the management of DH.

MATERIALS AND METHODS

A double blind randomized clinical trial was carried out over a period of 12 months following approval from the Institutional Ethics Committee [IEC/C/72/2013/DCT/dated 09-12-13] and Clinical Trials Registry of India (CTRI). The reference population was patients suffering from DH. Patients reporting to outpatient section of the Department of Conservative Dentistry and Endodontics constituted the source population. The study population was selected from the source population based on the inclusion criteria described by Holland (7). Only those subjects who were willing to provide informed consent were included in the study.

COMPOSITION OF THE TOOTHPASTES

1. Colgate Sensitive Pro-Relief toothpaste contains 8% arginine bicarbonate, calcium carbonate, sorbitol, sodium lauryl sulphate, flavor, sodium silicate, sodium carboxymethyl cellulose, sodium monofluorophosphate, sodium bicarbonate, titanium dioxide, potassium acesulfame, xanthan gum, sucralose, in aqueous base
2. Acclaim toothpaste contains 1% Nano-hydroxyapatite, sorbitol, glycerin, silica, purified water, cocamido propyl betaine, hydroxy ethyl cellulose, titanium di-oxide, flavoring agents, sodium saccharin.

SAMPLE SIZE CALCULATION

A minimum sample size of 15 in each group was calculated using data from previous studies (6, 8).

The minimal relevant difference (MIREDIF) used in these calculations were 0.595.

Power of our inter group comparison results calculated is 99%.

To increase the power of the study and to compensate for possible dropouts during the study period, it was decided to include more patients (30 in each group).

SAMPLE SELECTION AND INTERVENTION

Subjects were randomly allotted to group 1 or group 2 with an allocation ratio of 1 : 1. Blocks of random numbers were assigned using computer generated tables. To ensure that the principal investigator and the study subjects were not involved in the allotment of treatment arms, random numbers were generated and allocated by a clinician not involved in the study. Blinding was achieved by wrapping the two dentifrices under study.

Eligibility for recruitment into the study was assessed at the screening visit. A single tooth was evaluated in a subject. In individuals with multiple cervical abrasions, a single tooth was randomly chosen. The tooth to be tested was isolated using cotton rolls. To identify a tooth with DH, two stimulus tests were performed with an interval of 5 minutes between the tests (9).

1. Tactile test: An explorer was gently run across the affected tooth surface (Fig. 1A).

2. Air blast test: A blast of air from a three-way dental syringe for one second (Fig. 1B).

The subjects were asked to score the elicited pain based on the VAS (Fig. 2) and those indicating a score greater than 2 were included in the trial. 95 patients were assessed for eligibility and 60 patients were selected for this study into two groups.

Group I: 30 patients assigned to use dentifrice containing arginine.

Group II: 30 patients assigned to use dentifrice containing nHA.

The electrode of the digital electric pulp tester was placed on the selected tooth (Fig. 1C) and the current required for eliciting a VAS score of 2 was recorded before application of dentifrice. The electrical pulp tester was applied to the abraded area of the tooth in all patients. Digitest II (PARKELL, Inc., New York) was the pulp test-

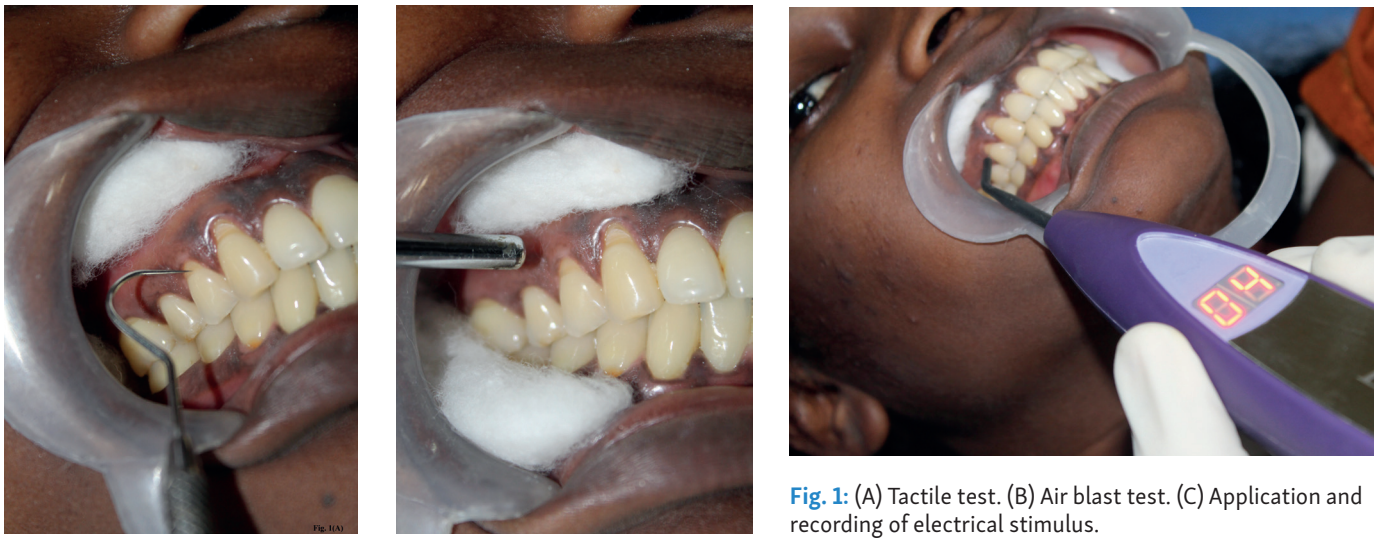

Fig. 1: (A) Tactile test. (B) Air blast test. (C) Application and recording of electrical stimulus.

er used. One cm of toothpaste was then expressed on the tooth surface for two minutes in each group and rinsed off. The electrical stimulus required to elicit a VAS score of 2 was recorded after 5 minutes to assess the immediate relief from DH.

To assess the effectiveness at the 1st and 4th week, the patients were provided with dentifrices to be used at home regularly for 4 weeks and no other oral hygiene measures were to be used during this period. The patients were instructed to apply 1cm of toothpaste directly on the sensitive site of the selected tooth using a soft brush for 1 minute followed by brushing for 2 minutes twice a day. They were given proper oral hygiene instructions including tooth brushing techniques. At the end of 1st and 4th week, electrical stimulus measurements to elicit a VAS score of 2 were made.

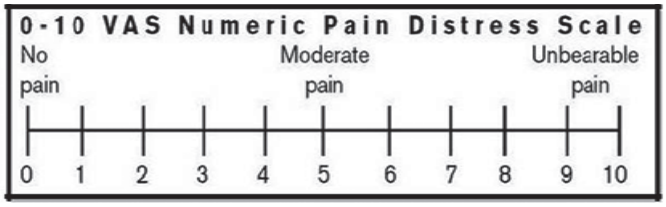

Fig. 2: Visual Analog Scale (VAS).

PRIMARY OUTCOME

The primary outcome was the electrical stimulus reading as provided by the digital pulp tester.

STATISTICAL ANALYSIS

Data was entered using Microsoft Excel and analyzed using SPSS (Statistical Package for Social Sciences) version 22.0. Shapiro-Wilk test was used to assess normality of the data. Descriptive statistics (mean & standard deviation) were calculated and the baseline characteristics were compared using Pearson's chi-squared test for qualitative and independent t-test for quantitative variables. To compare the effectiveness of dentifrices at different time intervals, independent t-test was used for inter group comparison and repeated measures analysis of variance (ANOVA) for within group comparison.

RESULTS

The present randomized clinical trial investigated the efficacy of two commercially available toothpastes in reducing DH. The improvement in DH was assessed clinically by measuring the change in amperage values over time using an electrical stimulus test. The CONSORT flowchart depicting the progress of subjects through the various stages of this trial is shown in Fig. 3. All the enrolled (n = 60) subjects completed the study. No adverse effects on the oral soft or hard tissues were observed by the examiner or reported by the participants.

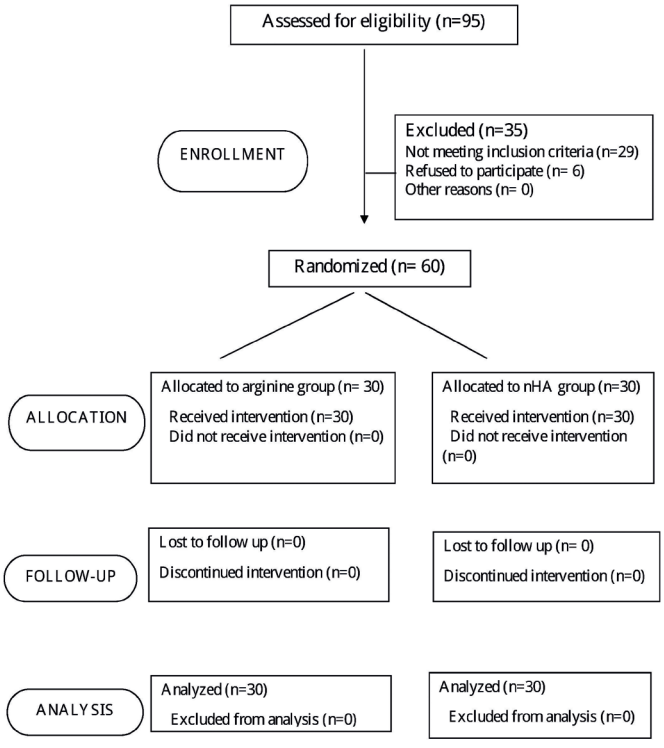

Fig. 3: Consort Flowchart.

Tab. 1: Comparison of baseline characteristics.

	arginine group	nHA group	P value
Chronological age	42.17 ± 7.344	42.33 ± 7.581	0.931[a]
Baseline amperage	6.27 ± 1.530	6.23 ± 1.251	0.927[a]
Gender distribution (males/females)	12/18	13/17	0.793[b]

a) Significance in t-test
b) Pearson chi-square significance

Tab. 2: Descriptive statistics of amperage values.

Group	Amperage reading at	Mean	SD
Arginine group	Baseline	6.27	1.53
	After 5 minutes	8.23	1.68
	After 1 week	9.87	1.48
	After 4 weeks	11.27	1.41
nHA group	Baseline	6.23	1.25
	After 5 minutes	8.27	1.34
	After 1 week	9.93	1.17
	After 4 weeks	11.53	1.33

Tab. 3: Statistical analysis of within group comparison.

Repeated measures ANOVA					
Group		**Paired differences**			
		Mean	**Confidence interval**		**Sig**
			Lower bound	**Upper bound**	
Arginine group	Amperage after 5 min-amperage baseline	1.97	1.65	2.29	.000
	Amperage after 1 week-amperage after 5min	1.63	1.29	1.98	.000
	Amperage after 4 week- amperage 1 week	1.40	1.08	1.72	.000
nHA group	Amperage after 5 min-amperage baseline	2.03	1.82	2.25	.000
	Amperage after 1 week-amperage after 5min	1.67	1.33	2.01	.000
	Amperage after 4 week- amperage 1 week	1.60	1.25	1.95	.000

Tab. 4: Statistical analysis for intergroup comparison.

Electrical stimulus reading	**Arginine group**		**nHA group**		
	Mean	SD	Mean	SD	Significance (independent t-test)
Amperage after 5min-Baseline amperage	1.97	.615	2.03	.414	.624
Amperage after 1week-Baseline amperage	3.60	.932	3.70	.794	.656
Amperage after 4week-Baseline amperage	5.00	1.017	5.30	1.022	.259

BASELINE CHARACTERISTICS (TABLE 1)

Descriptive statistics (mean and standard deviation) of the baseline variables were calculated. The gender distribution in the two groups were analyzed using Pearson chi-squared test which showed no significant difference (P = 0.793).

Independent t-test was done to assess the difference in mean age between the groups and was found to be not statistically significant (P = 0.931). The values were compared using independent t-test. No statistical difference was observed between the two groups (P = 0.927). Thus, the baseline variables of the two groups were comparable in all the characteristics.

WITHIN GROUP COMPARISON (TABLE 2, TABLE 3)

To test the significance of this difference in amperage readings, repeated measures analysis of variance (ANOVA) was used. The significance level was set at 0.05 and Bonferroni correction was applied to eliminate the error factor associated with multiple comparisons. Statistical analysis of intragroup comparison showed that the mean difference was highly statistically significant (P = 0.000) in both groups (Table 3).

INTERGROUP COMPARISON (TABLE 4)

The mean change in amperage values from baseline at 5 minutes, 1 week and 4 weeks between two groups were analyzed

using student t-test. Since there was no statistically significant difference between the two toothpastes at any of the time intervals, the null hypothesis stands accepted.

DISCUSSION

DH is one of the most common painful conditions of vital teeth associated with exposed dentin that affects approximately 33% of the population and is of multifactorial etiology (10). Two treatment modalities are currently utilized to manage this condition. The first is based on the occlusion of patent exposed dentinal tubules, causing alteration of fluid flow and reducing hydraulic conductance (11). The other option is the blocking of pulpal nerve response with ions which reduce intra-dental nerve excitability by depolarization, which interrupts the transmission of pain stimuli (12).

DH is primarily treated with tubular occlusion procedures using cavity varnishes, bonding agents and restorative resins. Although laser therapy has gained some popularity, it has disadvantages like complexity of use and high cost (13). Toothpastes have the benefit of low cost, ease of use and at-home application (14).

Advances in dentifrice technology have focused on creating dentifrices which works by tubular occlusion. One such toothpaste based on Pro-Argin technologyTM has been developed utilizing the physiological action of the amino acid, arginine (5). Another recently available formula is based on nanotechnology, which delivers hydroxyapatite nanocrystals, thereby causing tubular occlusion (6). There have been a number of studies supporting the superiority of arginine and nHA containing dentifrices over the popular desensitizing toothpastes (6, 15). No studies have been reported to date comparing the effect of arginine and nHA containing dentifrices and hence the rationale for the study.

The present randomized clinical trial investigated the effect of two commercially available toothpastes – containing 8% arginine and 1% nHA in reducing DH. As the aim of this study was to compare the reduction in dentin hypersensitivity between the two toothpastes, control group with placebo was not included in the study. Tooth sensitivity was measured using an electrical stimulus which provided an objective assessment of reduction in DH. The methodology consisted of a progressive elevation of the magnitude of the electrical stimulus until a sense of prepain rather than pain was felt. Electric pulp tester was used to utilize the advantage of an objective assessment of DH. Amperage readings were recorded before treatment and at three time points following dentifrice application – at 5 min, 1 week and 4 weeks of treatment. Oral self-care was standardized since brushing technique and frequency has significantly high correlation with hypersensitivity (16). The patients were instructed to brush twice daily for 4 weeks using only the particular dentifrice provided and a soft toothbrush.

There was a progressive increase in amperage values from the preceding appointment at each time intervals tested in both the groups as shown in Table 2. This indicated that both arginine and nHA dentifrices were effective in the reduction of DH, which in turn can be attributed to an increasing degree of tubular occlusion at successive appointments.

Within group comparison of amperage, readings showed statistically significant difference within both the groups (P = 0.000). The progressive increase in amperage values over time is suggestive of a cumulative effect of the toothpastes tested in the reduction of DH. The results showed that both toothpastes provided instant and lasting relief from DH. An interesting finding of our study was a reduction in the difference in amperage values between successive appointments as shown in Table 3. It can be suggested that the highest amount of relief from hypersensitivity is obtained in the immediate phase of dentifrice application.

Furthermore, the nHA group showed consistently higher reduction in DH at each of the time intervals as shown in Table 3. This could be due to the superior remineralization potential of nHA which has been clinically proven. This difference in reduction of DH was however not found to be significant statistically.

In the present study, 79% reduction in DH was obtained by electrical stimulus assessment at 4 weeks with arginine containing dentifrice and was comparable with the results obtained by Kleinberg et al. (5). Docimo et al (17) has reported a reduction of 11–38% only, which is not comparable to the present study. Thomas Schiff et al. (18) as well as Ayad et al. (8) obtained much higher reduction in DH as compared to the 79% reduction in DH in our study. This variability may be due to difference in the stimulus tests applied.

The combination of arginine and calcium carbonate acts by forming a plug that occludes the dentinal tubules. The positively charged arginine is attracted to the negatively charged dentin surface, where it promotes adhesion of calcium carbonate to the dentin surface and deep into the tubules. The association of the arginine and calcium carbonate in situ provides an alkaline environment which encourages endogenous calcium and phosphate ions to deposit and occlude the dentinal tubules (19).

The promising results of nHA toothpaste obtained in our study were substantiated by the studies done by Shetty et al. (20), Michele Vano (14) and Gopinath et al. (21). Using a double-blind, randomized design, Orsini et al. (6) compared a dentifrice containing nHA with potassium nitrate/fluoride dentifrice. In the present study, 85% reduction in DH was obtained by electrical stimulus assessment at 4 weeks which was greater than the findings of Orsini et al. (6). This variability can be attributed to the difference in the methodology followed.

The desensitizing effect of nHA crystals is due to the closure of dentinal tubules with plugs of HA within a few minutes and regeneration of a mineralized layer in a few hours (22, 23, 24). Roveri et al. (23) described deposition of HA on the enamel or dentin surfaces filling the pits and scratches thereby sealing the exposed dentinal tubules. Another reason for the reduced DH experienced by the subjects using the nHA dentifrice could be due to the lower abrasion value in relative dentin abrasivity (RDA) of about 23 compared to dentifrices containing silica (RDA 37.5) (25, 26).

Our study findings confirm the clinical effectiveness of both arginine and nHA containing toothpastes as desensitizing agents. The results are in accordance with several studies using different assessment tools.

However, this study is not without drawbacks. The difference in the readings in the EPT may not necessarily represent remineralization of dentinal tubules alone. A positioning gig would have been ideal to allow accurate reproduction of the site of application of the probe. We have to also acknowledge the inherent difference in response to noxious stimuli between individuals. This might have influenced the results. In addition, as with any prospective clinical trial of this nature, the possibility of Hawthorne effect could have also biased the participants of this study.

CONCLUSIONS

It appears from this study that both nHA based and arginine based tooth pastes are useful in the management of dentin hypersensitivity. Future studies with larger sample size preferably with patient centered quality of life based outcome measurements should be conducted in testing the efficacy of products used to treat dentin hypersensitivity.

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Bilateral Simultaneous Testicular Torsion in a Newborn: Report of a Case

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ABSTRACT

Introduction: Testicular torsion is a urological emergency. If not recognized in time, this condition may result in ischaemic injury and loss of testis. Simultaneous bilateral neonatal testicular torsion is extremely rare and is usually misdiagnosed.

Case report: We report a case of a male newborn, who presented with bilateral scrotal swelling and redness of the scrotum. Doppler ultrasound supported the diagnosis of bilateral testicular torsion, with an absent blood flow signal on the right side and a weak signal on the left side. Testicular exploration through scrotal incision was performed and bilateral testicular torsion was found. Right testis was grossly gangrenous, and right orchiectomy was performed. Left testicle was dark but showed recovery after detorsion with some bleeding from incised tunica albugenia. Fixation of the left testicle was performed. At six month follow-up, the left testis showed signs of atrophy and hormonal assay showed very low testosterone and elevated LH and FSH, suggesting hypogonadism.

Conclusions: Management of neonatal testicular torsion is a matter of controversy. Testicular torsion results into acute ischemia and urgent surgical exploration is the key point of management. Although the possibility of salvaging the involved testicles is usually very low it is hard to justify a passive approach to a bilateral torsion resulting in such a devastating condition as anorchia.

KEYWORDS

testicular torsion; neonatal torsion; newborn; bilateral testicular torsion; simultaneous testicular torsion

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INTRODUCTION

Testicular torsion refers to the torsion of the spermatic cord structures and subsequent loss of the blood supply to the ipsilateral testicle. This is a urological emergency; early diagnosis and treatment are esential for saving the testicle and preserving future fertility. Unfortunately there may be a lack of awareness among physicians or parents with regard to this urological emergency, and in most cases the diagnosis is deferred (1). Annual incidence of testicular torsion is 4.5 in 100,000 males 1–25 years of age (2). It can occur at any age but usually occurs in young males, with a bimodal incidence in the pediatric population: during the first year of life, and between the ages of 13 and 16 (1, 2). Bilateral cases account for 2% of all torsions, and simultaneous bilateral testicular torsion is extremely rare (3). It is a commonly held belief that a testicle torsed for longer than 6 h is outside the survival time-frame (1–3). If treated within 6 h of the presenting pain, there is a good chance of saving the affected testicle, as 90–100% testicles will be saved. If treated within 6–12 h 20–50% testicles will be saved and if treated within 12–24 h 0–10% testicles will be saved (2). Neonatal testicular torsion is a rare event with controversies regarding its etiology, presentation, surgical management and sequelae (4). It may be unilateral or bilateral. Bilateral torsion may be synchronous or asynchronous. The time when the torsion occurred is very difficult to determine; it has been reported to occur antenatally as well postnatally (5). Usually it affects healthy full term newborns, but it has been reported in preterm infants also. Definitive diagnosis is difficult to make without scrotal exploration (4, 5). The pediatric urologist or pediatric surgeon is usually consulted in the first few hours of life and is faced with formulating the management plan. There is much controversy regarding the optimal management.

Here, we present a case of simultaneous bilateral testicular torsion of the testicles in a newborn.

CASE REPORT

A male newborn, weighing 3430 g, was the product of a full-term, uncomplicated vaginal delivery. There were no signs of distress and no abnormalities were noted except diffuse swelling and redness of the scrotum, more evident on right side. The testes were hard and tender on palpation. The abdomen was soft and not tender on palpation. Bowel sounds were presented and there was no evidence of inguinal hernias. The white blood cell count was 18.40 × 10^9/l (normal range; 6.2–17.8 × 10^9/l) and C reactive protein level was 16.6 mg/l (normal range; 0.1–4.1 mg/l). All other laboratory examinations showed normal values. An ultrasound of the abdomen showed normal findings. Doppler ultrasound of the scrotum, showed heterogeneous tissue image of the right testicle. Hydrocele with absent blood flow of the right testis was also found (Fig. 1a). Left testicle was swollen and peripheral subcapsular arterial blood flow was presented (Fig. 1b). Bilateral scrotal exploration was performed through scrotal incision and revealed bilateral testicular torsion. A 720° counterclockwise extra-vaginal torsion of the right testicle was found with obvious gangrene of the right testicle. Thrombosis of the spermatic blood vessels distally to the site of torsion was also found (Fig. 2a). The left testicle was found to have a 270° counterclockwise extravaginal torsion, testicle was dark but showed recovery after detorsion with some bleeding from incised tunica albugenia (Fig. 2b). Right orchiectomy was performed with fixation of the left testicle.

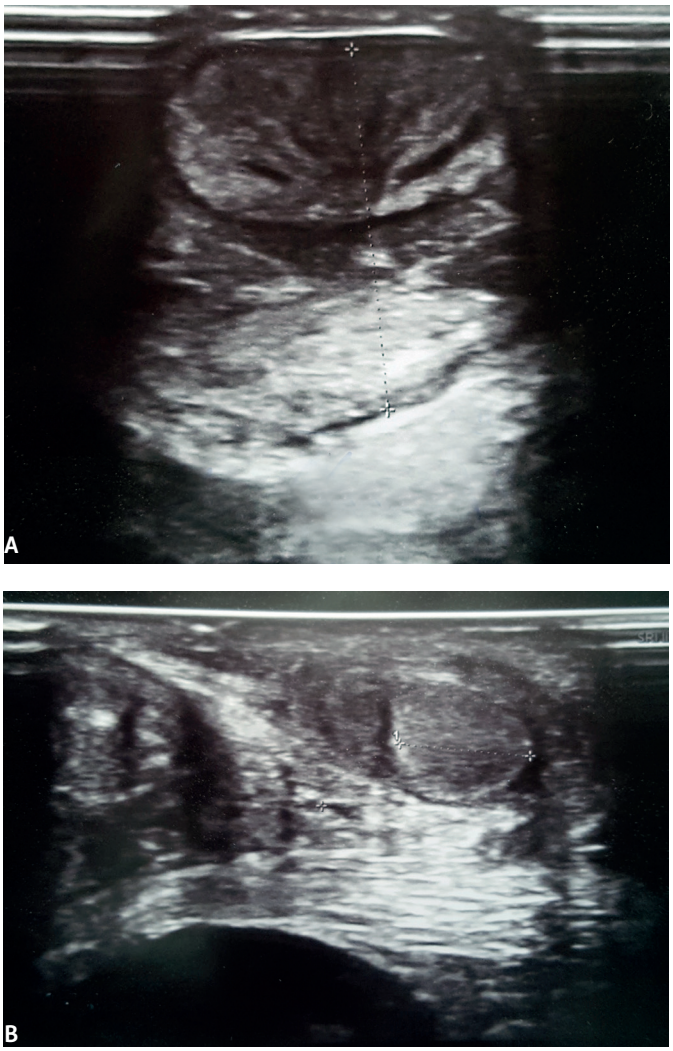

Fig. 1: Ultrasound of the scrotum: A) Heterogeneous hypoehogenic tissue of the right testis; B) Swollen left testis.

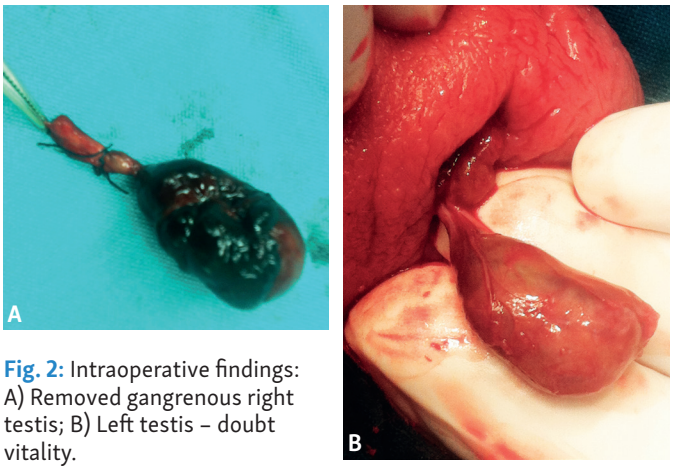

Fig. 2: Intraoperative findings: A) Removed gangrenous right testis; B) Left testis – doubt vitality.

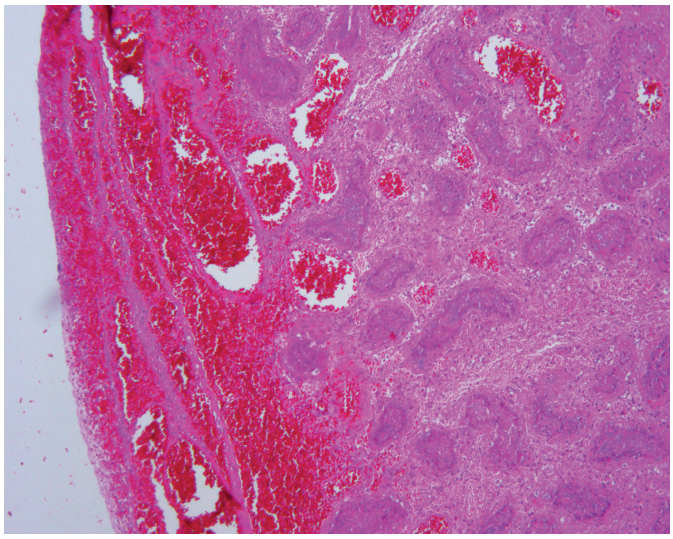

Fig 3: Necrotic testicular tissue, permeated with blood, and severe stagnation of blood in blood vessels (HE × 100).

Histological examination confirmed hemorrhagic necrosis of right testicle (Fig. 3). Follow-up at one month showed that the left testicle was smaller in size without detected testicular blood flow by Doppler ultrasound. However, at six month follow-up, the left testicle showed signs of atrophy and hormonal assay showed very low testosterone and elevated LH and FSH, suggesting primary hypogonadism. The patient was referred to an endocrinologist for further treatment and possible substitution of testosterone.

DISCUSSION

Both intrauterine and postnatal testicular torsion result with extra-vaginal torsion which is a different entity than the intra-vaginal type but has the same devastating consequences if not diagnosed and managed in time. Testicular torsion results with acute ischemia and its sequelae such as abnormality of testicular function and fertility. Urgent surgical exploration and fixation of the other testis are the key points in the management. Neonatal testicular torsion represents about 12% of all testicular torsions during infancy (4). It is thought that the majority (70%) of perinatal torsions are present at delivery and 30% develop postnatally in the first month of life (6). The clinical features are usually present since birth, but are often unnoticed on time. Epididymitis, scrotal hemathoma or pyocele may simulate testicular torsion in the neonate. Diagnosis is in many cases made based on a high degree of suspicion and from the clinical features alone. Color Doppler ultrasound, testicular isotope scan or MRI, may support the clinical diagnosis, but rarely preclude scrotal exploration especially in the neonate (6, 7). Controversy exists concerning the urgency of exploration. Many studies recommend that in newborns who present with suspected unilateral testicular torsion within the first 30 days of age, the risks associated with early surgery and anesthesia outway the prospect of salvaging the testis (4). It is now clear that the potential untoward anesthetic risks involving an otherwise healthy neonate quoted in prior studies are outdated and are not consistent with the current standards of pediatric anesthetic practice (8). There is difference between an acute torsion presenting after birth and the more common entity of the long standing event of antenatal testicular torsion. Das and Singer reported the results of a survey of pediatric urologists and literature review and concluded that early operative intervention with orchiectomy and contralateral orchidopexy was the preferred management strategy for cases of suspected neonatal torsion because surgical exploration was the only definitive way to establish the diagnosis and rule out other potential pathological conditions. They also found that in boys with neonatal torsion, at least 28% occurred postnatally (6). This suggests a potentially greater rate of testicular salvage than the disappointing results previously reported. Pinto et al. reported salvage rate of 20% with emergent surgical exploration (9). While there is a theoretical possibility that retention of the infarcted testis may result in some hormonal production, in bilateral testicular torsion it is wise to preserve the least infarcted testicle. Another reason to remove the infarcted testicle is to minimize the chance of aptoposis of the germinal epithelium in the contralateral testicle (5). Many authors adopted the policy of early surgical intervention (5, 8, 10, 11). John et al. reviewed the literature on neonatal testicular torsion. They described 77 boys treated for neonatal torsion, and no testicles were salvaged (12). This dismal outcome underlines that immediate surgical exploration, although commonly performed may not save torted testicles. Reports of neonatal simultaneous bilateral testicular torsion are limited on few case reports, mostly describing lack of diagnosis and poor outcome (5, 10–12). Clinical judgement by a pediatric surgeon or urologist is of outmost importance, not the ultrasound. Although the prognosis for these patients is poor, an elective delay in operative intervention seems to be inappropriate from medical and medicolegal point of view. Taking the risk into consideration, bilateral emergent exploration is still strongly advised in all neonates.

CONCLUSIONS

Neonatal bilateral perinatal testicular torsion is a rare event and it represents a true emergency due to the high risk of hypogonadism. Establishing a correct and fast diagnosis as well as the emergency bilateral surgical exploration are essential in the attempt to save the testicular function. Our recommendation is that in any suspicion of bilateral perinatal torsion of the testicles a bilateral exploration be carried out.

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A Rare History: an Intracranial Nail Present for Over a Half-Century

Ozkan Durmaz[1], Ali Karadag[2,*], Fusun Demircivi Ozer[2], Mahmut Camlar[2], Erik H. Middlebrooks[3], Baran Bozkurt[4], Mehmet Senoglu[2]

ABSTRACT

We present a rare case of a patient with a persistent headache for many years found to have an intracranial nail present for nearly 65 years. The nail was found entering approximately 1 cm from the midline on the left side, passing below the superior sagittal sinus, with the tip 1.5 mm right of the frontal horn of the lateral ventricle. Treatment strategies designed to optimize outcome for intracranial foreign bodies and possible complications are discussed in this report. We also discuss the decision for surgical intervention for foreign bodies and the relevance of position of the foreign body.

KEYWORDS

nail; penetrating injury; headache; intracranial

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INTRODUCTION

In the general public, penetrating injuries are less common than many other traumatic injuries, such as blunt trauma (1, 2). The incidence of penetrating skull and head injuries is ~0.4% of all head injuries. It has been estimated that penetrating injuries from nails constitute 33.3% of all penetrating injuries (3). Penetrating injuries are commonly accidental, but inflicted injuries, such as stabbings, firearm injuries, homicide, or suicide attempts are also encountered (4). Penetrating head injuries due to a foreign body may result in no lasting neurologic deficit but frequently result in significant morbidity or mortality. The complications can range from intracerebral hematoma, intraventricular hemorrhage, cerebral contusion, pneumocephalus, brain stem injury and carotid sinus fistula, amongst others (5–7). Injuries to the intracerebral vasculature and infections are the major cause of death (8–10). Our case is interesting because the patient lived more than half of a century with a nail in her brain with persistent headaches being the only symptom.

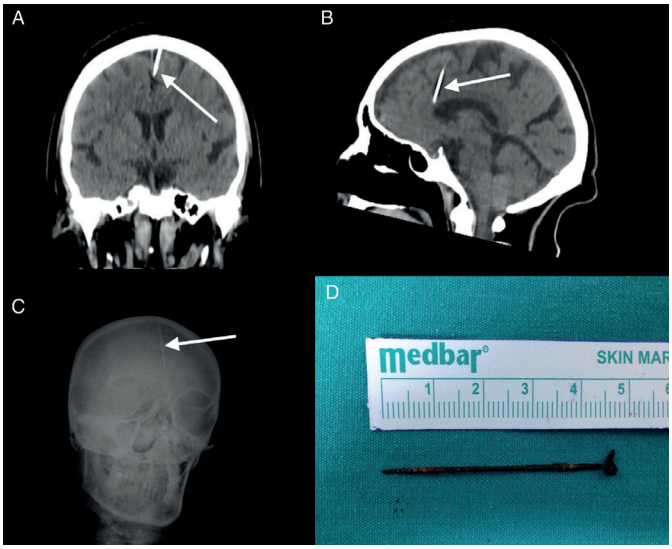

Fig. 1: Preoperative CT scan images in the coronal (A) and sagittal (B) plane show the course of the intracranial nail (arrow). AP radiograph (C) also illustrates the relationship of the nail (arrow) with the skull. The nail (D) was surgically removed through a burr hole.

CASE REPORT

We report the case of a 66-year-old female admitted to neurosurgery with persistent headaches for nearly 65 years. Her family reported no known accidents or head traumas throughout her life. At the time of admission, the findings included persistent frontoparietal headache, blood pressure of 125/75 mmHg, pulse rate of 82 beats/min (bpm), respiratory rate of 20 breaths/min, and body temperature of 37.1 °C. She was conscious, cooperative, and well oriented to time, place, and person with no weakness or neurological deficits. Routine laboratory results were normal.

Computed tomography (CT) of the head without contrast was performed, which revealed the presence of a linear, metallic foreign body nearly 4.5 cm in length. On physical examination, the nail was not palpable under the scalp. The coronal CT images of the brain show the nail penetrating the frontal lobe through approximately 4.5 cm of brain parenchyma (Figure 1A). The nail entered nearly 1 cm from the midline on the left side of the frontal lobe. It crossed the falx cerebri obliquely under the superior sagittal sinus and reached the frontal horn of the right lateral ventricle. The distance between the tip of the nail and the anterior edge of the frontal horn, as seen on sagittal CT images, was 1.5 mm (Figure 1B). The nail is also shown on a skull radiograph as a 4.5 cm metallic foreign body entering the calvarium through the left frontal bone (Figure 1C).

Following the CT, we hospitalized the patient and completed the preparations for surgery. We made a burr-hole near the nail inlet and extended it. A mini-dura-mater incision was made and overthrown to the midline. Following this incision, the nail (Figure 1D) was visualized and removed. The dura-mater and skin were sutured. Postoperative head CT showed the presence of small metal-density fragments in the area of the removed nail (Figure 2). Given the appearnce of the removed nail, this was felt to represent small corroded and rusted debris from this old nail. The patient was placed on antibiotics (ciprofloxacin and ceftriaxone) and followed up 2 weeks post-operatively. She was in good condition and did not have any neurological deficit on examination. Her headache gradually resolved.

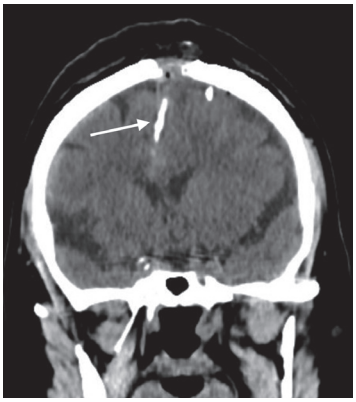

Fig. 2: Postoperative coronal CT image shows postoperative changes from burr hole and nail removal with residual metallic debris within the area of nail removal (arrow). The was felt to be from small corroded and rusted metal fragments.

DISCUSSION

Penetrating injuries are most commonly accidental and only sporadically reported (11). Less frequently, these injuries are a result of attempted suicide, stab and goneshot wounds, a nail wound to the head, armed conflict in civilian/military areas, child abuse, or attempted infanticide (12, 13). This study reports an interesting case of a nail in the intracranial cavity for more than half of a century. In the absence of known head trauma, and based on patient discussion, it was hypothesized that our case was the result of a form of infanticide wherein a foreign body is inserted through the fontanelle into the brain (14).

An interesting observation from our case is the absence of serious complications or neurological symptoms despite the presence of a metallic foreign body in her brain for approximately 65 years. The only symptom was a persistent headache. Imaging revealed that the tip of the nail was lo-

cated near the edge of the right lateral ventricle without breach of the ventricular wall. It is possible that the lack of penetration of the non-sterile nail into the cerebrospinal fluid circulation reduced the likelihood of disseminated central nervous system infection (15).

Surgical management of intracranial foreign bodies is not straightforward and must be assessed on a case-by-case basis (16, 17). The standard management of penetrating intracranial injury is to fully assess the depth and location of the penetrating object with imaging, followed by a decision whether surgery is appropriate. The most important concern with penetrating intracranial objects is the potential injury to vascular structures. The treatment, whether surgical or not, should always include antibiotic treatment (7). Prophylactic use of antiepileptic drugs is controversial (18).

In our case, we believed surgery to be appropriate since the patient experienced persistent symptoms of headache. The aim of our surgery was maximum protection of neural function with minimization of complications. Based on previously discussed surgical consideration, we believed the risk of complications was low given the location and suspected ease of removal of this foreign body. The potential for surgical risk and perceived benefit must be weighed closely in such cases. Patients should be informed about the potential outcomes and allowed to make the final decision. In our case, the patient elected surgical intervention, which resulted in no neurologic complications and reduction in the patient's symptoms.

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Rare Abdominal Wall Malformation: Case Report of Umbilical Cord Hernia

Andro Gliha[1,*], Andrija Car[1], Stjepan Višnjić[1], Bozidar Zupancic[1], Karmen Kondza[2], Ivan Petracic[1]

ABSTRACT
The umbilical cord hernia is the rarest form of abdominal wall malformations, anatomically completely different from gastroschisis and omphalocele. It occurs due to the permanent physiological evisceration of abdominal organs into umbilical celom and persistence of a patent umbilical ring. The umbilical cord hernia is often mistaken for omphalocele and called "small omphalocele". Here we present a case of a female newborn with umbilical cord hernia treated in our Hospital. After preoperative examinations surgery was done on the second day of life. The abdominal wall was closed without tension. The aim of this article is to present the importance of the proper diagnose of these three entities and to stimulate academic community for the answer, is this umbilical cord hernia or small omphalocele.

KEYWORDS
umbilical cord hernia; omphalocele; gastroschisis; abdominal wall malformation

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INTRODUCTION

The umbilical cord hernia, gastroschisis, and omphalocele comprise the group of congenital malformations of the ventral abdominal wall. The umbilical cord hernia is the rarest form of these malformations, anatomically different from gastroschisis and omphalocele. It occurs due to the permanent physiological evisceration of abdominal organs into umbilical celom and persistence of a patent umbilical ring (Figure 1). Gastroschisis occurs due to the evisceration of abdominal organs through the defect of the abdominal wall on the side of the obliterated right umbilical vein, always to the right of the umbilical cord (Figure 2). Omphalocele occurs because of an anomaly in the lateral folding of the embryonic disc during the formation of the abdominal wall (1) (Figure 3). The Umbilical cord hernia is often mistaken for omphalocele, but unlike omphalocele, the hernia is a smaller defect with a normal, physiological insertion of the umbilical cord and formed muscles of the abdominal wall. Omphalocele is a more serious defect of the abdominal wall, with eviscerated abdominal organs covered with amniotic membrane, with the more lateral insertion of the muscles of the abdominal wall to the thorax. Newborns with omphalocele have the worst prognosis due to the high rate of related congenital and chromosomal anomalies. The biggest macroscopic difference between omphalocele and umbilical cord hernia is the recognizable umbilical cord insertion, which, in the case of omphalocele, is at any part of the amniotic membrane, as compared to the dermal fold around the umbilical ring in umbilical cord hernia (2).

It is important to properly diagnose the three entities to ensure proper treatment and prognosis.

CASE REPORT

A female newborn was born in the 39th week of gestation by an emergency C-section due to fetal hypoxia and bradycardia, and it was referred to our hospital with a diagnosis of omphalocele. Apgar was 7/9, birth weight 3010 grams, length 50 centimeters, and head circumference 36 centimeters. The omphalocele was suspected during the 11th week of gestation on the ultrasound examination, with a later seen cyst of the umbilical cord. Prenatally, there was a suspected type II agenesis of the ductus venosus. Due to common congenital anomalies and chromosomal aberrations in children with ompalocele, a chorionic villus sampling in the 12th week of gestation showed a normal female karyotype. The omphalocele and cyst of the umbilical cord were monitored until birth.

A check-up of the newborn established a diagnosis of umbilical cord hernia instead of omphalocele. The clinical status was dominated by a centrally positioned smaller abdominal wall defect, 3 centimeters in diameter. The hernia sac was located above the defect and it contained vital loops of the small and large intestine. Above the hernia sac, extending from the umbilical cord, there was a cyst filled with clear yellowish fluid. The insertion of the umbilical cord and its blood vessels was physiological, but there were only one vein and one artery present. We found dermal fold around the umbilical ring, typical for umbilical cord hernia. Otherwise, there was a slight head dysmorphia (dominant neurocranium, prominent frontal eminence, lower set of auricular and saddle nose) and a skin covered intergluteal groove in the sacral region of the vertebrae.

The following day, surgery was performed under general anesthesia. The hernia sac was accessed through the lower edge of the cranial side of the hernia sac. During exploration, loops of the small and large intestine were found adherent in a few places to the inner wall of the hernia sac. We didn't find associated anomalies of the intestines. After adhesiolysis, the contents of the hernia sac were returned to the abdomen without resistance, followed with complete excision of the hernia sac. The abdominal wall was closed without tension. The navel was reconstructed using Steri-strip (Figure 1).

Early post-operative course was uneventful. Peristalsis was present from the second post-op day, and peroral feeding started on the third post-op day.

A comprehensive check-up was conducted: cardiologist, neuro-pediatrician, EEG poligraphy, neurosurgeon, radiological check-up, orthopedist, physiatrist, ENT, geneticist. There was generalized hypotonia, dysmorphia with less severe dysplastic features. Ultrasound examination of the heart showed an open ductus arteriosus, foramen ovale and mild mitral insufficiency.

The child was released to home care on the eighteenth post-op day with regular weight gain, appetite and bowel movements. She is regulary followed up. Ultrasound examination of the heart still showes open foramen ovale, without previously mentioned open ductus arteriosus and mild mitral insufficiency. Despite the last normal physical and neurological finding, she is still under neuropediatrician and physiatrist care due to earlier deviation in her development and hypotonia. MRI of the brain was preformed due to ultrasound finding of the hypoplasia of the corpus callosum, which showed normal brain development. EEG showed normal brain activity. Genetic tests were normal, with chromosomal microarray analysis still in progress.

DISCUSSION

Umbilical cord hernia is the rarest form of ventral abdominal wall anomalies that is embryologically and anatomically different from gastroschisis and omphalocele. Unlike omphalocele which appears in the earliest stages of embryonic development – during the folding of the lateral folds and the forming of the peritoneal cavity – the umbilical cord hernia appears later when the peritoneal cavity has already been formed (1). Physiological evisceration and rotation of the intestine into the umbilical celom takes place from the 5th to the 12th week of gestation. Umbilical cord hernia appears into the 10th to 12th week of gestation, when the return of intestinal loops from the umbilical celom into the peritoneal cavity is terminated (1). Umbilical cord hernia is characterized by a milder defect to the abdominal wall, 2–3 cm in diameter, centrally positioned next to the physiological insertion of the umbilical cord, as shown in Figure 1. Hernial sac contains the loops

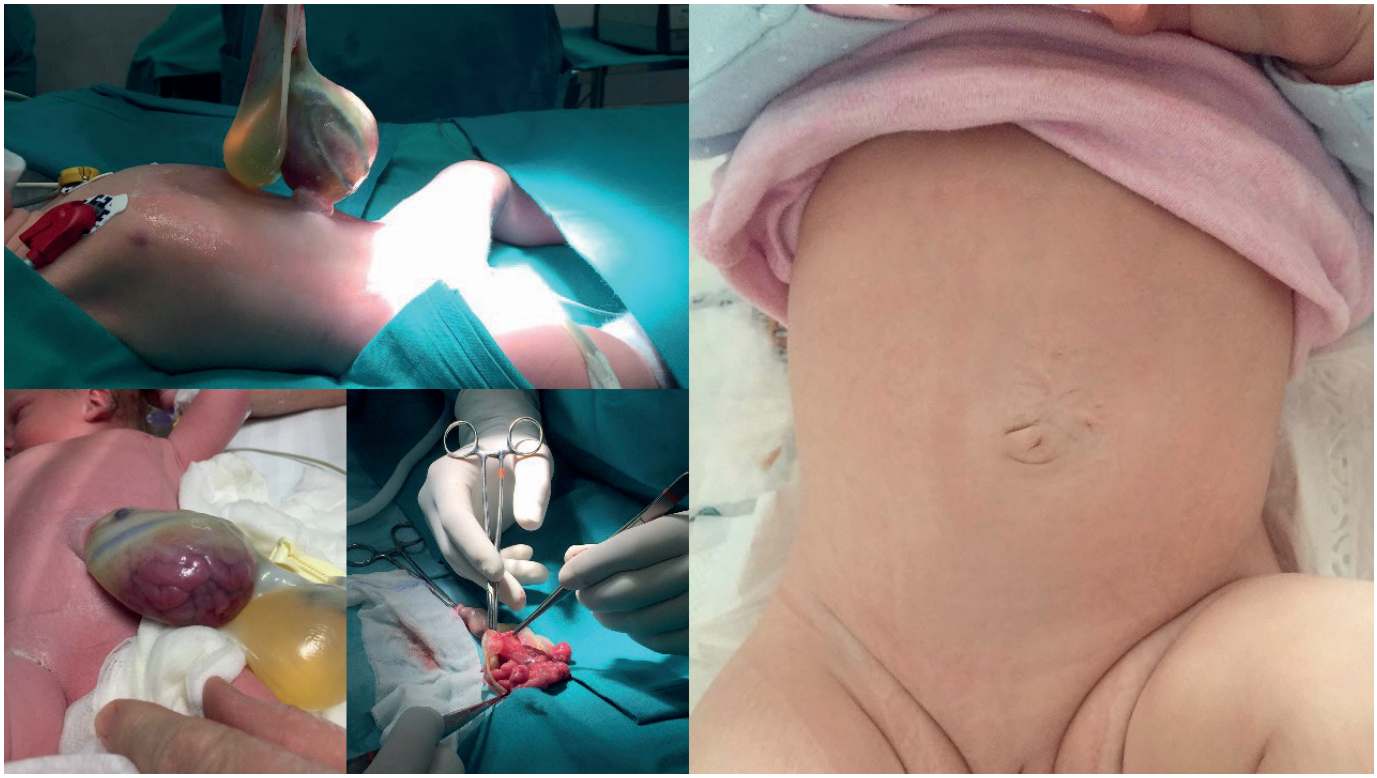

Fig. 1: Umbilical cord hernia.

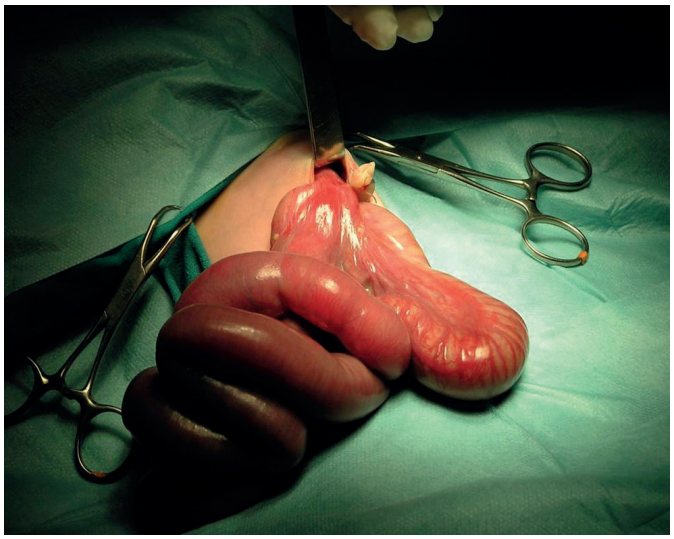

Fig. 2: Gastroschisis.

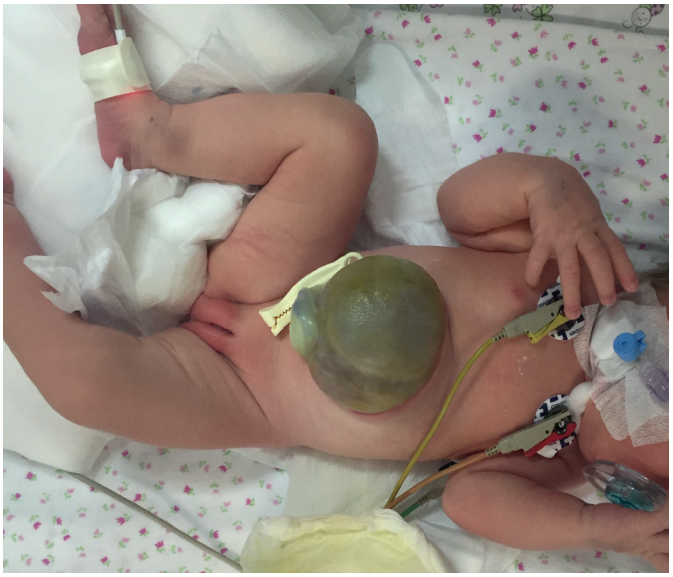

Fig. 3: Omphalocele.

of both the small and the large intestine and rarely the liver and the gallbladder. Associated anomalies and chromosomal aberrations happen rarely, as shown by Haas et al, who described a series of 7 newborns with umbilical cord hernia whose amniocentesis had normal karyotype, as in our case (2, 3).

The navel was reconstructed by turning the skin in the anatomic region of the umbilicus using forceps and fixing it with Steri-Strip without using stitches. That resulted in a more cosmetically pleasing look of the umbilicus when compared to the reconstruction using purse string stitching.

Umbilical cord hernia belongs to the same group of defects that also includes omphalocele, and is often misdiagnosed as a small omphalocele (4, 5). The aim of treatment is the same, reconstructing the ventral abdominal wall while repositioning the abdominal organs into the abdomen. However, the prognosis is different due to the higher occurrence of associated congenital and chromosomal anomalies in children born with omphalocele. Moreover, there is a well-documented risk of iatrogenic injury to the intestinal loops in the hernia sac while clamping the umbilical cord (6).

In conclusion, there is a clear difference in the onset and outcome of umbilical cord hernia when compared to omphalocele which is often accompanied by congenital anomalies and chromosomal aberrations. The prenatal diagnosis of omphalocele may cause the parents to feel uneasy and anxious, as well as make them decide on ar-

tificial abortion (3). Such a destiny would be a tragedy for any family, because the termination of a pregnancy with maximal chance for healthy life of the child would be performed. A much higher awareness about this entity is needed among the caregivers to prevent from deleterious effects of false decision making.

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Amyand's Hernia: an Up-to-Date Review of the Literature

Dimitrios Patoulias[1,*], Maria Kalogirou[2], Ioannis Patoulias[2]

ABSTRACT
Amyand's hernia is defined as an inguinal hernia, containing the appendix within the hernia sac. Incidence of this rare condition rises up to 1% (0.19–1.7%) of all inguinal hernia cases. Inflammation of the appendix within the inguinal sac is even rarer, as it corresponds to 0.1% (0.07–0.13%) of all Amyand's hernia cases. After a comprehensive review of the limited relevant literature, we aim through this review study to describe the pathophysiology of inflammation of the appendix – contained in the hernia sac – and present the latest data about the diagnostic approach and surgical treatment of Amyand's hernia.

KEYWORDS
inguinal hernia; appendix; acute appendicitis; appendectomy; child

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DEFINITION AND HISTORY

Amyand's hernia is defined as an inguinal hernia, containing the appendix within the hernia sac. In 1735 C. Amyand described the first case of incarcerated inguinal hernia, containing a perforated appendix, in an 11-year-old boy (1). The patient underwent simultaneous ligation of the hernia sac and appendectomy. Historically, it was the first conducted appendectomy (2). It should not be confused with femoral hernia containing the appendix. The latter was named De Garengeot hernia after Rene Jacques Croissant De Garengeot, who first described in 1731 a case of femoral hernia, containing a non-inflamed appendix (1, 3).

EPIDEMIOLOGY

It is more common in childhood, given that inguinal hernia is, mainly, caused by a persistent patent processus vaginalis (PPV). Amyand's hernia cases have been recorded in every age, from neonates to elderly (4). Amyand's hernia corresponds to 2% of all appendectomies, during neonatal period and infancy (5). It is, understandably, more frequent in males, due to the greater incidence of inguinal hernia, and right-sided (4). A left sided Amyand's hernia is usually the consequence of the mobile cecum syndrome and presence of sizeable appendix. However, in theoretical basis, it can be present on a background of situs inversus or malrotation (2, 3, 5, 6, 7). In a review of 30 cases, 3 out of 30 were left-sided (8). According to Kinoo et al., only 15 left-sided Amyand's hernia cases were reported, until 2013 (2). Nicola et al. and Mahajan et al. described cases, in which Amyand's hernia was accompanied with the bladder, ovarian, fallopian tube, omentum or a Meckel diverticulum. Cecum is the organ that is most frequently contained within hernia sac (9, 10). Additionally, in cases of complete appendiceal protrusion within the sac, at least a part of the cecum protrudes, as well.

PATHOPHYSIOLOGY

Amyand's hernia occurs in 1% (0.19–1.7%) of all inguinal hernia cases (2, 3, 6, 11). In 0.13% of all cases, the appendix is inflamed. It should be noted that appendiceal perforation leads to a dramatic increase of the mortality rate (15–30%), due to severe abdominal sepsis (2, 3, 6, 12).

The incidence of acute appendicitis in the general population is 8%, whereas- as mentioned above – incidence of appendicitis present in an inguinal hernia is reported to be 0.1% (12, 13). The exact mechanism of appendicitis, within an inguinal hernia is not fully understood (5). After a thorough review of the existing literature, some opinions are reported below:

(1) Incarceration and, subsequently, inflammation of the appendix (14, 15).

(2) The presence of the appendix within the hernia sac predisposes for the development of adhesions between its serous membrane and the hernia sac, resulting in an irreducible hernia, susceptible to injury (6, 16).

(3) The contraction of anterolateral abdominal muscles leads to an increase in intra-abdominal pressure, causing compression and functional obstruction of the prolapsed appendix (17).

(4) Inflammatory swelling of the appendix may be the beginning of a vicious cycle. Thus, Amyand's hernia becomes irreducible, accentuating the swelling due to venous stasis and causing an impaired microcirculation of the appendix wall, resulting in bacterial overgrowth and translocation (11, 12).

CLINICAL PRESENTATION

This entity is usually asymptomatic, presenting with the typical symptoms of inguinal hernia in childhood (reducible – usually, automatically – bulge of the groin with local mild discomfort). In very rare cases, incarceration and obstruction of the appendix may be induced, resulting in acute appendicitis (18, 19). Given that the inflamed appendix is contained within the hernia sac, the symptoms of the appendicitis, in this case, are those of an irreducible or incarcerated inguinal hernia or, occasionally, of an acute scrotum ipsilaterally with the inguinal hernia, with accompaning symptoms such as pain in the right lower quadrant of the abdomen, anorexia, nausea and vomiting (20, 21, 22). During physical examination, common findings include a painful, irreducible bulge in the groin area, accompanied with swelling of the overlying tissue and excessive redness of the overlying skin. Typically, McBurney sign is absent in those patients (23, 24). Differential diagnosis should include hydrocele, testicular torsion, inguinal lymphadenitis and epidydimo-orchitis (10).

DIAGNOSIS

In most cases, Amyand's hernia is diagnosed intra-operatively (5, 6, 25). Sharma et al. treated 18 patients with Amyand's hernia, while no patient was diagnosed pre-operatively (6, 26). Cankormaz et al. treated 12 neonates and infants (median age = 40 days) with Amyand's hernia, making the diagnosis pre-operatively in one out of twelve cases (22). Weber et al. performed a retrospective study of 60 Amyand's hernia cases, treated over 12 years, out of which the hernia was diagnosed in only one of them (14).

In certain cases, the performance of imaging -such as ultrasound or computed tomography (CT) could provide useful information substantial for preoperative diagnosis (6, 27). Okur et al. studied 21 Amyand's hernia cases, performing a preoperative ultrasound in 12/21 cases (57.1%) and diagnosing the hernia in 9/12 (75%) of them (11).

Most surgeons do not recommend imaging examination in the context of preoperative evaluation, in order to proceed with surgical repair of an inguinal hernia, especially when there is indication of prompt therapeutic intervention. We believe that a symptomatic incarcerated or difficultly reducible inguinal hernia should be investigated via imaging studies, aiming at increasing the number of complicated Amyand's hernia cases being preoperatively diagnosed.

The most significant ultrasound finding is the presence of a non-compressible tubular structure within the hernia sac. In case of appendicitis, additional features include wall thickening and hyperemia (20, 28).

The primary CT signs considered as pathognomonic for Amyand's hernia are a blind ending tubular structure inside the hernia sac, arising from the base of the caecum, wall thickening, hyperemia and periappendiceal fat stranding (12, 20).

THERAPEUTIC STRATEGY

Losanoff and Basson proposed a classification for Amyand's hernia, setting a therapeutic framework (Table 1) (20, 29, 30, 31).

Tab. 1: Losanoff and Basson classification of Amyand's hernia.

Classification	Description	Management
Type 1	Normal appendix in an inguinal hernia	Hernia reduction, mesh replacement
Type 2	Acute appendicitis in an inguinal hernia with no abdominal sepsis	Appendectomy, primary no prosthetics hernia repair
Type 3	Acute appendicitis in an inguinal hernia with abdominal and abdominal wall sepsis	Laparotomy, appendectomy, and primary no prosthetic hernia repair
Type 4	Acute appendicitis in an inguinal hernia with abdominal concomitant pathology	Same as type 3 plus management of concomitant disease

Tab. 2: Classification of Amyand hernia after Rikki modification.

Classification	Description	Management
Type 1	Normal appendix in an inguinal hernia	Hernia reduction, mesh replacement
Type 2	Acute appendicitis in an inguinal hernia with no abdominal sepsis	Appendectomy, primary no prosthetics hernia repair
Type 3	Acute appendicitis in an inguinal hernia with peritoneal and/or abdominal wall sepsis	Laparotomy, appendectomy, and primary no prosthetic hernia repair
Type 4	Acute appendicitis in an inguinal hernia with abdominal concomitant pathology	Same as type 3 plus management of concomitant disease
Type 5a	Normal appendix within an incisional hernia	Hernia reduction, primary repair of hernia including mesh replacement
Type 5b	Acute appendicitis within an incisional hernia without peritonitis	Appendectomy through hernia, primary closure of the aponeurotic gap, no prosthetics hernia repair
Type 5c	Acute appendicitis within an incisional hernia with peritonitis or abdominal wall sepsis or in relation to previous surgery.	Management as type 4

Singal et al. refer to the modification of the Losanoff and Basson classification of Amyand's hernia, also known as Rikki modification. A fifth type of Amyand's hernia is added on the latter classification, referred as an incisional hernia through which the vermiform appendix protrudes. This type is divided into three subtypes, 5a, 5b and 5c (Table 2) (30).

As a general rule, in case of a non-inflamed appendix, the patient undergoes hernia repair without appendicectomy (12, 19, 22, 31). Researchers sharing this opinion believe that this approach could decrease postoperative complications, as a clean surgery is not converted to a clean-contaminated one. Besides, the appendix could be used, in the future, for replacement of the extra-hepatic biliary tract, urinary diversion or appendicostomy (Malone procedure) (9, 33). Furthermore, during appendicectomy, surgical manipulations in the base of the caecum could increase the recurrence rate of the inguinal hernia, due to detachment in the deep inguinal ring (32). It should be noted that surgical manipulations involving the appendix could trigger secondary acute inflammation (32, 33). This – theoretical – possibility is minimized, when the procedure is performed laparoscopically (9, 33). Shaknovsky et al. refer to the successful treatment of an adult patient with Amyand's hernia type I, after application of Robotic platform Da Vinci Surgical System' 3D HD imaging (34).

Exception to this rule is an non-inflamed appendix contained in a left-sided Amyand's hernia, where preventive appendectomy is recommended, as, in case of a future appendicitis, there is a high risk of false or delayed diagnosis or even resistive surgical procedure (8, 12, 35).

We believe that algorithmic approach of Amyand's hernia, as described in schema 1, is a safe guide as for choice of the appropriate therapeutic strategy (Schema 1).

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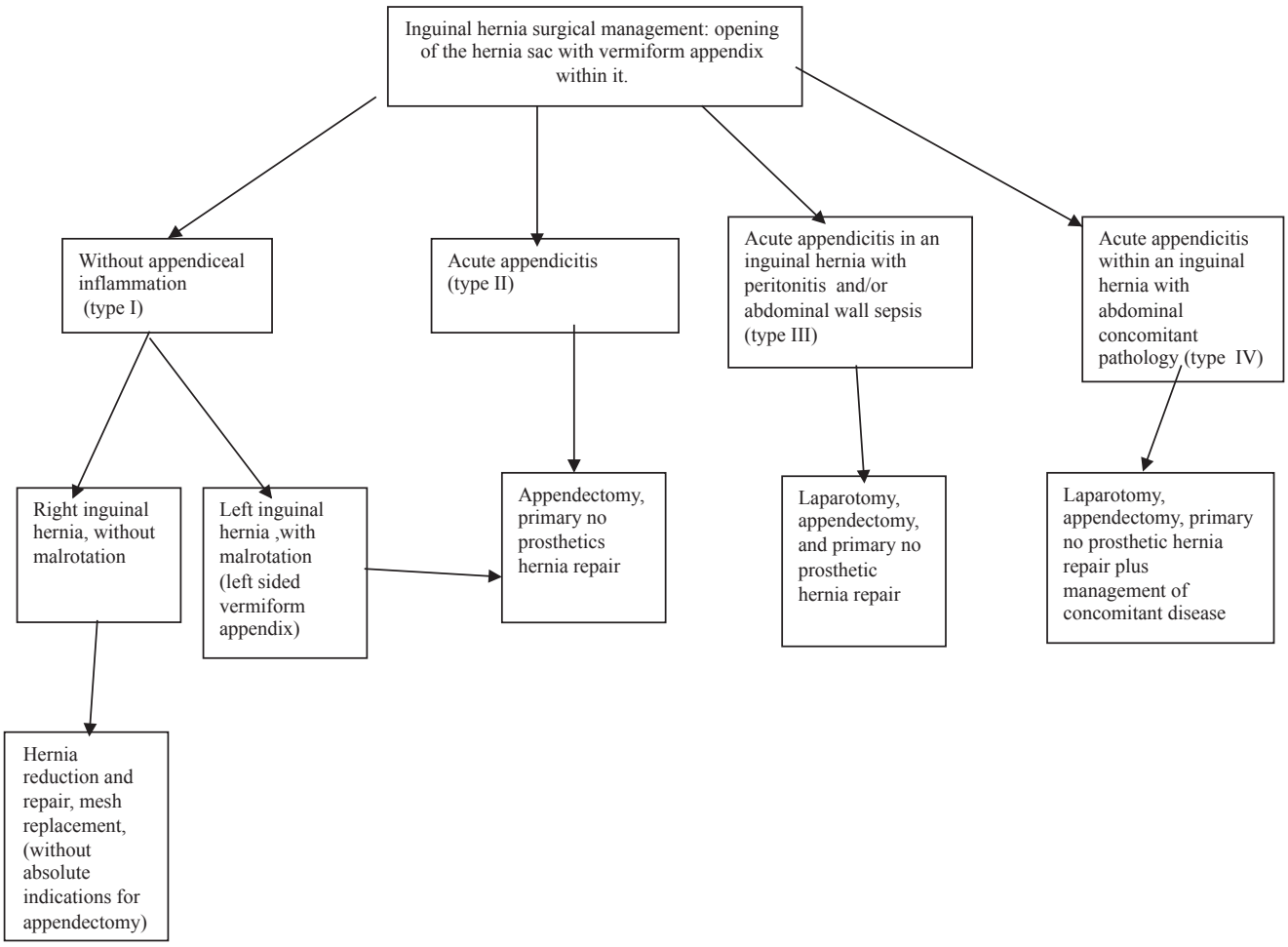

Schema 1: Algorithmic therapeutic approach of Amyand's hernia.

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