RAPID C-REACTIVE PROTEIN AND WHITE CELL TESTING DECREASES COSTS AND SHORTENS STAY IN PEDIATRIC EMERGENCY ROOM

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Syventävien opintojen kirjallinen työ
Tampereen yliopisto
Lääketieteen yksikkö
Tammikuu 2014

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Kirjallinen työ, 18 s.
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Tammikuu 2014

Avainsanat: C-reaktiivinen proteiini, kustannussäästöt, lastenpäivystys, pikatesti, vieritesti, valkosolumäärä

Merkittävä osa lasten päivystyksellisistä käynneistä terveydenhuollon toimipisteissä johtuu infektiotaudista tai sen epäilystä. Veren kohonneita valkosolu (leukosyytti)- ja CRP-pitoisuuksia pidetään yleisesti epäsuorana viitteenä bakteerin aiheuttamasta elimistön tulehdustilasta. Viime vuosina sairaaloiden päivystyspoliklinikoilla yleistyneet valkosolujen ja CRP:n pika- eli vieritestit on aikaisemmissa tutkimuksissa osoitettu tarkoiksi ja luotettaviksi testimenetelmiksi, mutta niiden taloudellisesta vaikutuksesta ei ole tutkimustietoa. Pikatestien etuna on yksinkertainen näytteenotto, joka ei vaadi koulutettua laboratoriohenkilökuntaa sekä muutamien minuuttien kuluessa näytteenotosta valmistuva testitulos, mikä mahdollistaa nopeiden hoitopäätösten tekemisen ja saattaa lyhentää potilaan polikliinistä hoitoaikaa.

Tämän tutkimuksen tarkoituksena oli arvioida pika-CRP- ja pikaleukosyyttimittausten kustannuksia verrattuna perinteisin laboratoriomenetelmin tehtyihin mittauksiin sekä selvittää vieritestauksen vaikutusta lapsipotilaiden hoitoaikaan päivystyspoliklinikalla.

Tutkimusaineistona käytettiin retrospektiivisesti kerättyjä 166 lapsen sairauskertomustietoja ajanjaksolta elokuu 2012 - lokakuu 2012. Tampereen yliopistollisen sairaalan potilastietojärjestelmästä poimittiin niiden lasten tiedot, joiden diagnostiikassa oli päivystyspoliklinikalla käytetty pika-CRP- tai pikaleukosyyttimittausta. Pikatestauksen taloudellista vaikuttavuutta arvioitiin vertaamalla pikatestien käytöstä aiheutuvien kulujen määrää niihin kuluihin, jotka olisivat kertyneet mikäli vastaavat testit olisi tehty laboratoriossa. Hoitoaikaa tarkasteltiin suhteessa päivystyspoliklinikalla annettuun hoitoon ja tehtyihin lisätutkimuksiin.

Pikatestien kustannusten havaittiin olevan 41,5% vastaavien laboratioriotestien kustannuksista. Niiden potilaiden hoitoaika, joita ei pikatestien ohella tutkittu lisää ja jotka eivät saaneet välittömiä hoitotoimia päivystyspoliklinikalla, oli merkitsevästi lyhyempi kuin niiden potilaiden, joille tehtiin lisätutkimuksia tai jotka saivat välitöntä hoitoa päivystyspoliklinikalla (mediaani 147,5 vs. 201,5 min, $p< 0,001$).

Tutkimuksen perusteella CRP- ja leukosyyttiarvojen pikamääritys on kustannusvaikuttavaa ja oikein kohdistettuna lyhentää hoitoaikaa lasten päivystyspoliklinikalla.

SISÄLLYSLUETTELO

Käsikirjoitus on lähetetty julkaistavaksi elektronisessa muodossa Acta Paediatrica-lehteen 29.11.2013.

Rapid C-reactive protein and white cell testing decreases costs and shortens stay in pediatric emergency room

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Running title: Rapid testing of C-reactive protein and white blood cells

Conflicts of interest: None

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MS Eeva Kokko was primarily responsible for reviewing the hospital charts of the patients, the outcome assessment, data analysis and writing the manuscript. Prof. Matti Korppi contributed to the development of the protocol, analytical framework for the study and writing the manuscript. Dr. Merja Helminen provided statistical information and attended writing. Dr. Nina Hutri-Kähönen supervised the design and execution of the study and contributed to writing the manuscript.

Abstract

Aim: To evaluate how rapid testing of C-reactive protein (CRP) and white blood cells (WBC) influences the patient flow and costs in the pediatric emergency room (ER).

Methods: The study was a retrospective chart review. In all, 166 children who were treated during three months in the ER of a children´s hospital, and in whom rapid tests for WBC and CRP were done, were included. The association between rapid testing and the length of ER stay was evaluated, and their costs were compared with corresponding costs if done in hospital laboratory.

Results: The median ER stay lasted 147.5 min, if no other examinations than rapid CRP and WBC tests were taken and if no emergency treatments were given, compared with 201.5 min in those with other laboratory tests obtained or emergency treatments given ($p<0.001$). The respective figures were 142.5 and 179.5 min in those 96 children discharged home ($p=0.003$). The costs of rapid testing were only 41.5 % of the corresponding costs in laboratory.

Conclusion: The simultaneous rapid testing of CRP and WBC in children with presumable infection decreased the costs and shortened the length of ER stay if no other tests or emergency treatment in the ER were needed. The costs of rapid testing were only 41.5 % of the corresponding costs in laboratory.

Key words: C-reactive protein, Cost-effectiveness, Pediatric Emergency Room, Rapid test, White blood cell count

Key Notes: The costs of rapid testing of CRP and WBC were 41.5 % of the corresponding costs in laboratory. The median ER stay in 166 children admitted for presumable infections shortened 54 min (26.8 %), if no emergency treatment in the ER was needed and no other tests than rapid tests for CRP and WBC were done. The respective shortening in 96 children discharged home was 37 min (20.6 %).

[Introduction]

Elevated white blood cells (WBC) in peripheral blood and C-reactive protein (CRP) in serum are often used as nonspecific markers for bacterial etiology of infection in children, although this association has been proven only in bacteremic and severe local infections (1-4). In a recent study from Norway including more than one million emergency room or home visits in children and adults, CRP was studied in 27 % of all contacts, especially in respiratory infections (55 %) and in infants (44 %), and particularly by young and inexperienced doctors (5). There is increasing evidence that the use of CRP in primary health care has decreased prescribing of antibiotics for adults with respiratory infection (6-8), but t in some studies clinical algorithms have worked better (9). Corresponding CRP data have not been published in children.

In western countries, rising costs of health care and health care reforms including centralizing of emergency treatment to less and larger units have forced to focus attention on more rapid and less costly methods than customary laboratory tests. In addition, the patient flow from the emergency room to home or to hospital should be rapid. There are no previous studies on patient flow in child patients.

In some recent years, auto-calibrated rapid test devices have become into clinical use. This approach has been called as rapid testing, bed-side testing, near-patient testing or point-of-care testing. These devices have been reliable for quantifying serum CRP concentration compared with laboratory tests in adults (10) and in children (11). However, less data have been published on the reliability of WBC rapid tests (12). Their use shortens the time from sampling to receiving ready test results to some minutes, and the decision-making process has accelerated *e.g.* in the treatment of pneumonia in adults (13) and in children (14).

The rapid test devices for CRP and WBC measurements have been in use in the ER of our children`s hospital since 2009. The aim of the present study was to evaluate the costs of rapid WBC and CRP testing, as well as the influence of rapid testing on the length of the ER stay in admitted children.

Study subjects and methods

The study was a retrospective hospital chart review. Patients who were treated in the ER of the Department of Pediatrics, Tampere University Hospital from 1 August 2012 to 31 October 2012, and in whom CRP and/or WBC was determined with rapid tests, were included in the study. One of the authors (EK) collected the data from the patient records and electronic files of the hospital. Since only register data were used without any contacts to the patients, the head doctor of the hospital gave the permission for the study.

Tampere University Hospital provides as an only hospital pediatric inpatient care and secondary-level outpatient care for a population of about 90,000 children less than 16 years old. On average, 6000 patients have been annually treated in the pediatric ER of the hospital, most of them during the infection season from November to February. Usually, the children are admitted by general practitioners or pediatricians working in the public or private primary care. The doctors working in the ER are usually junior physicians who are specializing in pediatrics.

The study period was selected to avoid major epidemics caused by respiratory viruses, such as influenza or respiratory syncytial virus in late autumn or winter. The doctors on duty were advised to use the rapid tests available in the ER, if they considered the measurement of WBC and/or CRP as indicated, and if it was unlikely that other blood tests were needed. The Afinion AS100 analyzer (Axis-Shield PoC AS, Oslo, Norway) was used for CRP and the HemoCue WBC device (HemoCue AB, Ängelholm, Sweden) for WBC measurement.

The measurement range of the CRP device is 5-160 mg/l. The analysis method is based on immunometric membrane through-flow assay, and the total assay time is four minutes. The measurement range of the WBC device is 0.3-30.0 x10E9/l. The WBC count is determined, after hemolyzing of red cells, by colour staining of white cells in a microcuvette. The result is ready in three minutes. A self-test for quality control is built-in in both devices, and in addition, the laboratory of the hospital studies monthly quality control samples for both CRP and WBC.

CRP and/or WBC rapid tests were studied in 175 children during the three-month study period.

Four cases were excluded, since the rapid test results could not be found although the tests had been performed. CRP results of 8 children with a rapid test performed with the same device in the primary care immediately before admission to the ER were included. WBC results were available in 171 and CRP results in170 cases. Those 166 children, in whom both WBCs and CRP had been studied, form the subjects of the present study.

The data collected from the patient records and electronic files of the hospital included the check-in and check-out times, ICD-10 diagnoses (Table S1), CRP and WBC rapid test results, treatments given in the ER, and information on the treatment place (home or hospital). Other diagnostic examinations, classified as other blood tests (venous blood samples) and radiological studies (chest radiographs) were also recorded. The stay in the ER was registered in minutes. The time of the day during which the patient came to the ER was classified into three categories (day time 8.00-14.59, evening time 15.00-20.59, and night time 21.00-7.59).

The costs of rapid CRP and WBC tests consisted of leasing and maintenance costs of the devices (66.70 euros for the Afinion AS100 CRP analyzer per month, and 56.70 euros for the HemoCue WBC analyzer per month) and the use of disposable cuvettes (2.50 euros each, two per patient). The laboratory price per sample is 1.30 euros for CRP determination and 1.55 euros for WBC determination during office hours, and 2.60 euros and 3.10 euros outside the office hours, respectively. In addition, there is a sampling fee of 7.50-22.50 euros depending on the time of the day.

We constructed a hypothetical and from the rapid testing point-of-view optimized group of 507 children admitted to the ER for respiratory infection, tonsillitis or fever without a focus, during the 3-month study period (Table S1). The number of 507 was a real one obtained from the patient files of the hospital. The group was constructed with two assumptions: rapid testing of CRP and WBC was performed in all hypothetical patients, and rapid testing was in most cases expected to be sufficient without a need for any other tests. However, other laboratory tests were expected to be taken in 58 cases (10.8%; the rate received from the 166 study patients with CRP $\geq$ 120 mg/l or WBCs $\geq$20x10E9/l).

The data were analyzed with the SPSS 20.0 statistical package (IBM SPSS Statistics). Exploratory data analysis revealed that the distributions of age, ER stay, CRP and WBC were non-normally distributed. Therefore, the results are expressed as medians, interquartile ranges (IQR) and ranges,

as well as in frequency and percentage distributions. The statistical significances of the differences were tested with the Mann-Whitney test for continuous and with the Chi square or Fisher`s tests for categorized variables. The costs of the rapid tests were compared with the calculated costs in the 166 patients, if CRP and WBC would have been studied in the laboratory. Further, the results were extrapolated to the hypothetical group of 507 children admitted during the study period.

Results

The study group consisted of 94 boys (57 %) and 72 girls. The median age was 1.5 years (IQR 0.62-3.18, range 0.02- 15.3). The check-ins happened during day time in 38.6 %, evening time in 41.6 %, and night time in 19.9 % of cases. Thus, 69.9 % of the patients were treated outside the office hours. The most common diagnosis was bronchiolitis, followed by upper respiratory infection (Table S1).

Ninety-four children (56.6 %) needed radiological or laboratory examinations or emergency treatment in the ER. Chest radiograph or blood tests in laboratory were studied in 51(30.7 %) cases (chest radiographs in 40 and blood tests in laboratory in 18 cases), and 66 (39.8 %) children needed emergency treatment (usually salbutamol or adrenalin inhalations).

The median ER stay was 181.5 min (IQR 135-255, range 15-1983). Children who were transferred to hospital or discharged home without other examinations than rapid tests taken and without any treatments given stayed (median) 147.5 min ($p<0.001$ *vs.* those with other examinations taken or treatments given) (Table 1).

In all, 96 (57.8 %) patients were discharged home from the ER, and in 61.7 % of them, rapid CRP and WBC tests were the only procedures done. The median ER stay was 142.5 min ($p=0.003$ *vs.* those with other examinations taken or with treatments given) (Table S2).

CRP was <20 mg/l and WBCs were <15x10E9/l in 52.4 % of the children. Either CRP was ≥120 mg/l or WBCs were ≥20x10E9/l in 10.8 % of the cases (Table S3).

Fifty-one (30.7 %) patients were examined with additional laboratory or radiological studies. Additional studies were obtained significantly less often only if CRP was <20 mg/l and WBCs were <15.0 x10E9/l (Table 2). If CRP was ≥20 mg/l or WBCs were ≥15.0 x10E9/l such association was not anymore present (Data not shown).

Obvious reasons for additional laboratory tests were CRP ≥120 mg/l or WBCs ≥20x10E9/l in 4 cases (Table 2), and an error (outside the measurement range) in the CRP or WBC device in 3 cases and abnormally low WBCs in 3 cases (Data not shown). An obvious reason for the examination of chest radiograph was CRP ≥120 mg/l or WBCs ≥20x10E9/l in 5 cases (Table 2).

In 166 cases, the costs of CRP and WBC rapid testing were 41.5 % of the costs of corresponding laboratory tests. The respective figure was 45.9 % in the hypothetical group of 507 patients (Table 3).

Discussion

There were two main results in the present study on the impact of rapid CRP and WBC testing in the pediatric ER. First, the costs of rapid testing were less than half of the costs if the corresponding tests had been made in laboratory. Second, the rapid testing seemed to shorten the length of ER stay.

The use of rapid tests decreased the costs in the pediatric ER to half when compared with tests in laboratory. This result was confirmed by constructing and analyzing a larger, hypothetical study group. The use of rapid testing may have an even greater impact on total costs if the reduction of unnecessary radiological examinations, over-use of antibiotics and unnecessary hospitalizations are taken into account. In a previous adult study (13), the use of bed-side CRP test was not associated with reduced hospitalization rate but influenced on taking of chest radiographs and starting of antibiotic therapy. In children, rapid testing of CRP and WBCs was useful in separation of bacterial from viral pneumonia (14). Two studies performed in primary health care have demonstrated that rapid CRP testing has been cost saving in adults with respiratory infection (6,7), due to less use of services from the regional laboratory in the study from Denmark (6) and due to less prescribing of antibiotics in the study from Norway and Sweden (7).

The use of rapid tests shortened the length of ER stay only if no other laboratory examinations and no emergency treatments were needed. This may be explained by the characteristics of the patients included in the study. The majority of them suffered from bronchiolitis, wheezy bronchitis or asthma exacerbation, often needing emergency treatment in the ER. To our knowledge, no previously published data are available on the influence of rapid CRP or WBC testing on the patient flow in the pediatric ER. Our results favor the determination of CRP and WBCs using rapid tests in

children admitted for respiratory infection to the ER, but to get real benefits, the use of additional laboratory tests should be minimized.

The rapid test devices were found as easy to be used, and non-interpretable results were seen in only 2.5 % of the measurements. In earlier studies, the agreements between rapid tests and laboratory tests for CRP and WBC have been good (10-12). Our finding, that in >10 % of cases both rapid and laboratory tests were used, indicates that more precise instructions ought to be given to the doctors on duty. For example, 35 % of the additional laboratory tests and chest radiographs were taken although rapid WBC and CRP tests were low.

The study design did not allow to evaluation the influence of rapid CRP or WBC testing on hospitalization rates or antibiotic prescribing. There is increasing evidence that making rapid CRP test in the primary health care or emergency room has decreased the prescribing of antibiotics for respiratory infection in adults (7,8,15). There is an urgent need for corresponding studies applying CRP rapid testing in children.

The results of the present study must be interpreted with caution. The design of the study was a retrospective chart review. On the other hand, this approach may be the only way to study the practices of health care. Unfortunately, rapid testing was performed only in about one-third of the eligible cases, but this observation is also a result to be taken into account when the practices are further developed.

In conclusion, quantifying the capillary blood CRP and WBC levels by the rapid testing technology is possible in a fast and reliable way. Since venipuncture is not needed, rapid testing can be done without trained laboratory personnel. Rapid testing is cost saving and can be time saving as well. The results encourage to the further use of the CRP and WBC rapid test devices in the pediatric ER, as well as in other health care units which treat acutely ill children.

Electronic supplementary material

Table S1. ICD-10 diagnoses of 166 study patients and 507 hypothetical patients.

Table S2. Length of ER stay, presented in relation to obtaining chest radiographs, laboratory examinations and emergency treatment in the ER among the 96 children treated at home.

Table S3. Comparison of categorized CRP and WBC results in 166 study patients.

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Table 1. Length of ER stay, presented in relation to obtaining chest radiographs, laboratory examinations and emergency treatment in the ER among 166 study patients.

Number of cases	**Median**	**Interquartile range Q1-Q3**	**Range**	**P-value**
Chest radiograph (N=40)	180.5 min	164-221	67-413	0.980
No chest radiograph (N=126)	183 min	130-264	15-1983	-
Laboratory examinations (N=18)	248.5 min	178-300	67-1983	0.013
No laboratory examinations (N=148)	177 min	132-242	15-981	-
Chest radiograph or laboratory examinations (N=51)	185 min	165-240	67-1983	0.190
No chest radiograph or laboratory examinations (N=115)	179 min	128-255	15-981	-
Emergency treatment (N=66)	204.5 min	170-264	90-981	0.001
No emergency treatment (N=100)	155 min	100-242	15-1983	-
Chest radiograph, laboratory examinations or emergency treatment (N=94)	201.5 min	167-264	67-1983	0.000
No chest radiograph, laboratory examinations or emergency treatment (N=72)	147.5 min	84-238	15-535	-

Table 2. Obtaining of chest radiographs and laboratory examination in relation to combined rapid CRP and WBC test results.

CRP and WBC results	**Chest radiograph obtained** (n=40)	**Laboratory tests obtained** (n=18)	**Chest radiograph or laboratory tests obtained** (n=48)	**P-value**	**No chest radiograph or laboratory tests obtained** (n=114)
WBC <15 x10E9/l and CRP <20 mg/l (n=87)	12 (13.8%)	6 (6.9%)	17 (19.5%)	0.002[1]	70 (80.5%)
WBC ≥20 x10^9/l or CRP ≥120 mg/l (n=18)	5 (27.8%)	4 (22.2%)	7 (38.9%)	0.362[2]	11 (61.1%)

[1] compared to children with WBC ≥15 x10E9/l or CRP ≥20 mg/l
[2] compared to children with WBC <20 x10E9/l and CRP < 120 mg/l

Table 3. Costs in 166 study patients and in 507 hypothetical calculated patients.

Patient groups	**Leasing costs + cuvettes**	**Costs of additional laboratory tests**	**CRP and WBC prices + sampling fees**	**All costs**
Laboratory testing n=166	-	-	3789 €	3789 €
Rapid testing n=166	1199 €	374 €	-	1573 €
Laboratory testing n=507	-	-	8821 €	8821 €
Rapid testing n=507	2904 €	1148 €	-	4052 €

Table S1. ICD-10 diagnoses of 166 study patients and 507 hypothetical patients.

Diagnosis	**Study patients (N=166)**	**Hypothetical patients (N=507)**
Bronchiolitis (J21.9)	51 (30.7%)	136 (26.8%)
Upper respiratory tract infection (J06.9)	19 (11.4%)	83 (16.3%)
Pneumonia (J18)	12 (7.2%)	54 (10.7%)
Wheezy bronchitis (J45.1)	12 (7.2%)	44 (8.7%)
Non-specified infection (B34.9)	10 (6.0%)	43 (8.5%)
Otitis media (H66.0)	10 (6.0%)	44 (8.7%)
Tonsillitis acuta (J03.9)	3 (1.8%)	49 (9.7%)
Non-specified febrile illness (R50.9)	4 (2.4%)	54 (10.7%)
Others [1]	45 (27.1%)	0 (0.0%)

[1] Pyelonefritis N10 (n=8), Non-specified symptoms R68.1 (n=4), Gastroenteritis A08 (n=3), Laryngitis J04 (n=3), Pneumococcemia A40.3 (n=2), Cystitis N30 (n=2), Unspecified urinary tract infection N39 (n=2), Infant regurgitation P92.1 (n=2), Nausea R11 (n=2), Medical observation Z03.9 (n=2) and 15 other sporadic diagnoses.

Table S2. Length of ER stay, presented in relation to obtaining chest radiographs, laboratory examinations and emergency treatment in the ER among the 96 children treated at home.

Number of cases	**Median**	**Interquartile range Q1-Q3**	**Range**	**P-value**
Chest radiograph (N=20)	172.5 min	146.75-207.25	100-413	0.404
No chest radiograph (N=76)	154.5 min	100-255	15-1983	-
Laboratory examinations (N=5)	181 min	144-1129.50	118-1983	0.235
No laboratory examinations (N=91)	155 min	110-240	15-535	-
Chest radiograph or laboratory examinations (N=24)	175 min	146.75-229.50	100-1983	0.172
No chest radiograph or laboratory examinations (N=72)	152 min	98.50-253.75	15-535	-
Emergency treatment (N=20)	190 min	158.25-285	115-385	0.008
No emergency treatment (N=76)	150 min	100-227	15-1983	-
Chest radiograph, laboratory examinations or emergency treatment (N=38)	179.50 min	149.50-271.50	100-1983	0.003
No chest radiograph, laboratory examinations or emergency treatment (N=58)	142.50 min	73.50-219	15-535	-

Table S3. Comparison of categorized CRP and WBC results in 166 study patients

		CRP					Total
		5-19 mg/l	**20-59 mg/l**	**60-119 mg/l**	**≥120 mg/l**	**Error[1]**	
WBC	**<15.0 x10E9/l**	87 (52.4%)	26 (15.7%)	8 (4.8%)	3 (1.8%)	1 (0.6%)	125 (75.3%)
	15.0-19.9 x10E9/l	9 (5.4%)	7 (4.2%)	7 (4.2%)	2 (1.2%)	0 (0.0%)	25 (15.1%)
	≥20.0 x10E9/l	4 (2.4%)	5 (3.0%)	3 (1.8%)	1 (0.6%)	1 (0.6%)	14 (8.4%)
	Error[1]	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)
Total		100 (60.2%)	40 (24.1%)	18 (10.8%)	6 (3.6%)	2 (1.2%)	166 (100%)

[1] Outside the determination range