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RESEARCH ARTICLE

CONSUMPTION OF ANALGESICS BEFORE A MARATHON AND EFFECTS ON INCIDENCE OF ADVERSE EVENTS: THE HANNOVER MARATHON STUDY.

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Abstract

Objectives: Athletes commonly ingest analgesic drugs before competition. Previous studies assume a prevalence of 50%. We examined incidence of analgesics consumption before a marathon and occurrence of adverse events.

Methods: The study was designed as a non-interventional cohort study. Data assessment was conducted using a questionnaire before Hannover Marathon 2013. Endpoints were intensity of analgesic consumption and incidence of adverse events in the cohort of analgesic users as compared to analgesics free cohort.

Results: 712 questionnaires (out of 1532 participants) were returned and 655 complete. 17% took analgesics prior to the marathon. Used analgesics were evenly distributed between Aspirin, Ibuprofen and Diclofenac. Most athletes wanted to prevent pain (41%) or to treat pain (56%). 3.6% of the participants took aspirin to avoid thromboembolic events. The Analgesic Group had a slightly increased risk of experiencing severe adverse gastrointestinal events, without significant differences between groups. Pain in joints and swollen joints occurred significantly less in often the Analgesics Group (8.1% vs 16.1%).

Conclusion: Use of analgesics before a marathon was less common than assumed, and occurrence of unintentional side effects was low. However, more comprehensive studies are necessary to assess the risks of analgesics when used in context of marathon running.

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Introduction:-

A growing number of athletes participate in marathons worldwide. Most competitions take place in the USA; in 2014, there were approximately 1,100 competitions counting 541,000 finishers (number of participants who reach the finish line) [1]. Despite the fact that physical activity to a certain extent results in a better health condition [2], it is also known that intense exercise such as a marathon is associated with a considerable amount of side effects such as musculoskeletal, gastrointestinal, cardiovascular and renal problems [3-10].

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Previous studies have shown that almost 50% of marathon participants ingested non steroid anti-inflammatory drugs (NSAID) before the race and, therefore, their risk of adverse events during or after the race was 5 times higher than for participants who had not taken NSAID [11]. Common reasons for the abuse of NSAID are a desire to prevent pain, to improve functional recovery and to reduce muscle soreness [12].

Adverse events of NSAID are generally associated with gastrointestinal symptoms, e.g., relatively mild ones such as dyspepsia, nausea or vomiting, but also more severe side effects such as gastrointestinal (GI)-bleeding. Additional side effects include renal failure, edema, liver function abnormalities or cardiovascular events [11, 12].

While moderate to medium intensity exercise is an excellent way of cardio protection, intense exercise increases the risk of sudden cardiac arrest, known as Pheidippides fate [7]. The reason for such a sudden death in apparently healthy marathon runners is a structural heart disease and cardiomyopathy [13,14]. A second mechanism is acute myocardial infarction due to coronary disease. Thrombosis in general appears to be a health risk caused by changes in hematological parameters [15]. As shown by Hanke and coworkers, there is an increase in platelet activation in marathon runners with a potential higher risk for thromboembolic events [16].

In addition, athletes are not only getting older but they also tend to have a longer medical history and a daily medication plan and, apparently, they might not take into account the several possible interactions of NSAID with their daily medication such as acetylsalicylic acid (ASA) or serotonin reuptake inhibitors (SSRI). For a physician, it is becoming more and more complex to assess risks and/or benefits of prophylactic use before physical exercise; in any event, most athletes do not even consult their physician with regard to this question.

The Hannover Marathon Study intends to examine incidence of analgesics consumption before participating in a race as primary end point. Furthermore, occurrence of adverse events was evaluated, serving as secondary end point. Data were compared between marathon runners who consumed analgesics (Analgesics Group - AG) and runners without analgesic consumption (Control Group - CG); specifically.

Methods:-

Study Population and questionnaire

The investigation was based on a questionnaire that was notified in advance via internet and email by the organizer of the Hannover Marathon 2013 and was further accompanied by information as to the purpose of the investigation, followed by a recommendation to participate in the study.

The questionnaires were made available by staff of Hannover Medical School and participants processed the questionnaires before the race and returned them to the staff. Only participants who had already finished at least one full marathon prior to the Hannover Marathon 2013 were permitted to participate in the study.

The following information were examined:

- Age, sex, running experience and training information;
- Medical history of participants and daily medication;
- Ingestion of analgesics in previous races, name of the drug and the individual reason for taking analgesics;
- Whether the analgesics was prescribed or at least advised by a medical doctor;
- Symptoms after previous marathon(s) in relation to ingested analgesics or, by contrast, symptoms experienced without pain medicine;
- Personal judgement of risks concerning analgesics and marathon running.

All questionnaires were anonymized and integrity of participants remained unimpaired. The protocol was approved by the Institutional Ethics Review Board (IRB).

All data sheets were checked for completeness and incomplete ones were sorted out.

Statistical Analysis:-

Data were collected with Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, WA, USA), and the statistical analysis was based on SPSS 22 (IBM, New York, NY, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). Depending on whether the participants had consumed pain medicine, the data were allocated to one cohort group: the Analgesic Group (participants who had taken pain medicine before a marathon on

at least one occasion) and the Control Group (participants who had never taken analgesics before a marathon). Both groups together were defined as primary population.

Cross tables and the χ^2 were used to analyze subgroups in order to establish relative risk differences and possible confounding factors.

A binary regression model was used to estimate ODDs, with a 95% confidence interval for side effects in subgroups. Statistical tests were two-sided, and p-values below 0.05 were considered to be statistically significant.

Results:-

A total of 712 questionnaires were returned to our staff before the race; 57 questionnaires (8%) were excluded due to missing data or illogical completion (e.g., has never started under the influence of analgesics in a marathon, but has taken analgesics to prevent pain).

Our study population represents 42% (655 out of 1532) of the participants in the Hannover Marathon 2013; 16% (n=111) used analgesics before this race or any other marathon in which they ever participated.

Background Epidemiology

Overall there was a larger number of men taking part in the marathon than women (525; 80% vs. 130; 20%) but relatively, a larger number of women was to be found in the Analgesics Group (AG) than in the Control Group ((CG) AG 28; 25% vs. CG 102; 19%). The average age was 45y, the average height 177cm and the average weight 74.5kg, evenly distributed in both groups. 96% of the overall participants were German nationals, whereas in AG, this was true for 92% only. Demographic data are displayed in table 1.

Medical History

177 (27%) of the runners had a medical disorder before participating in the marathon. Probability for a medical disorder was twice as high in AG compared to CG; n=44 (40%) vs. n=133 (24.4%) and p=0.0012 (CI 95 1.3-3.1). Prevalence of diseases is shown in figure 1.

A significant difference was shown for asthma; 9.9% in the AG vs. 3.5% in the CG p=0.0048 (CI 95 1.4-6.6). A heart attack was reported by two participants from AG, but none from CG, which results in an ODDs Ratio of 24 and p= 0.039 (CI 95 1.2-521). Migraine also showed a statistically difference between the two groups: 3.6% in AG and 0.36% in CG; p=0.008 (CI 95 1.8-53).

There was no statistically significant difference for thrombotic or embolic events, chronic pain, renal failure, GI ulceration, GI bleeding, bleeding in general and strokes – diseases that require a regular analgesic consumption or may be induced by consumption of analgesics.

11 participants reported a peptic ulceration (0.9% AG vs. 1.65 % CG). This is equivalent to an ODDs Ratio of 0.54 and shows that ulceration is even less probable in AG.

Medication before Running

N=111 (16.94%) runners took analgesics before participating in the marathon; 21.5 % of the women and 15.8% of the men. Mostly, analgesics were taken on race day only (81.98%), while only 2.7% of the participants took them on a daily basis. Overall, 111 runners who had taken analgesics, took them on average before 4.5 of their 20.9 finished marathons. Only 18.9% had a prescription for analgesics, which means that 81.1% bought them over the counter.

Most frequently used analgesic was Ibuprofen (36%); in second place follows ASA, if Aspirin® and other ASA are taken together (35.1%), followed by Diclofenac (27.9%) and Paracetamol (19.8%). Only 1.8% took other analgesic substances.

In AG (n=111), n=92 took only one analgesic and n=16 took two different analgesics; n=2 took three different analgesics and one runner started under the influence of four different analgesics.

Other Medication

Other medications were antihypertensives, thyroid hormones, diabetes medication and anticoagulation medication. 57 runners took such an "other" medication (14 in AG vs. 7.9 in CG). Every participant took no more than one other drug. Symptoms after the marathon were not significantly higher in case analgesics and another medication were combined: n=2 runners with another medication had symptoms vs. n=26 runners with no other medication (p=0.57 CI95 0.1-3.0).

Intention for Analgesic Consumption

It was possible for the runners to indicate more than one reason for taking analgesics. Most frequently mentioned reason was to prevent pain in muscles (29.7%), followed by preventing bone pain (19%) and joint pain (15%); 15% wanted to reduce pain in arms and legs; 16% wanted to reduce their headache and 16% wanted to reduce their joint pain. If all kinds of pain treatments are summed up, 56% of the runners who took analgesics intending to reduce a certain kind of clinical manifest pain and 41% of the runners were focused on pain prevention. 3.6% intended to prevent a myocardial infarction or a thrombosis.

Events During Marathon Race

29% of the participants reported about events during or after the race: 30% did so in CG, 25% in AG; (ODDs Ratio 0.8; p=0.96 CI 95 0.4-1.26).

Most common symptoms during the marathon were muscle pain and swollen joints with a significant higher occurrence in CG, if both symptoms are considered together. (8.1% AG vs. 16.1% CG p=0.032, CI 95 0.22-0.94).

There was no significant difference between the groups as to typical GI symptoms. Nausea tended to occur more often in AG. However, difference was not significant (4.6% vs. 2.7%).

The ODDs show that the risk for developing a peptic ulceration is statistically significantly increased in AG (1.8%) compared to CG 0% (p=0.03 CI 95 1.1-521).

In total, severe GI symptoms were rare; 4 runners reported a GI bleeding (1.8% in t AG vs. 0.36% in CG, no statistically significant difference).

A statistically significant difference appears when the severe GI symptoms such as vomiting, peptic ulceration and GI bleeding are summed up: AG 6.3% vs. CG 1.6% (p=0.007 CI 95 1.45-10.9).

Subjective Risk Assessment

72.18% of the overall participants declared that they considered it "very questionable" or "questionable" to ingest analgesics (45% AG vs. 89.9% CG) and 27.82% considered it "less questionable" or "harmless" to take analgesics before a marathon (55% AG vs. 10.1% CG).

Discussion:-

There are many reports written about professional and amateur athletes who take analgesics in order to enhance their performance up to even 75% of the athletes depending on the study [11, 17-20].

Küster et al. showed that more than 50% of participants in the Bonn marathon (Germany) take NSAIDs, showing a 4-10 times higher risk of experiencing severe side effects [11]. The Hannover Marathon Study showed different results – only 17% of the participants consumed an analgesic substance.

Effects on the Musculoskeletal System

One of the main reasons for the runners to take NSAID is to prevent pain (41%). It is also known that an inhibition of the cyclooxygenase slows down regeneration of the muscle [21]; Ibuprofen further does not reduce, but even increases oxidative stress, measured as an increase of F2-Isoprostan [22,23]. Late occurrence of muscle pain does not appear to be positively influenced by the consumption of NSAID [24]. However, primary muscle pain seems to be influenced by NSAID. Tokmakidis showed a significant reduction of muscle pain and also a reduction of the creatin kinase as a sign of destroyed muscle tissue [25].

Results of the Hannover Marathon Study are similar: They also show a significant reduction of muscle pain for AG (16.1%) in comparison to CG (8.1%) if swollen joints and pain of joints are summed up ($p=0.032$). O'Grady likewise confirmed that there is a reduction of muscle pain caused by NSAID. In addition, as regards the muscle biopsy, he could show that there are less inflammatory and fibrotic changes in the muscle compared to his control group [26].

Effects on the GI System

GI symptoms after a marathon are common due to the reduced blood flow in the guts; they are similar to adverse events induced by NSAID. Side effects such as nausea, heartburn, stomach ache and diarrhea are common in 30% of the participants after a marathon run [27]. Estimated occurrence of occult blood after a race varies between 8 and 85%, which is due to mechanical trauma as well as mesenteric ischemia [5]. Symptoms seem to be based on hormones, reduced blood flow and further, they appear to be reverse proportionally to the effort, excitation and speed of the runner [6, 28, 29].

The data of the Hannover Marathon Study show a much lower amount of side effects and no statistically significant differences between the AG (3.6%) and the CG (6%) for mild GI symptoms such as nausea, stomach ache and heartburn. However, the data show a significant increase from 1.6% to 6.3% of the risk for severe adverse events such as vomiting, peptic ulceration and GI bleeding after analgesics consumption.

It is already known that the risk for GI bleeding after NSAID consumption depends on how often the NSAID is consumed, the medical history of the patient and other medication. The risk can be elevated by two to eight times, in case the NSAID is taken on a daily basis or combined with ASA or SSRI [30-33]. In the Hannover Marathon Study, the ODDs Ratio for GI bleeding was 4.9 with no statistically significant elevation in AG, possibly due to rare consumption of NSAID in AG. Nevertheless, preemptive consumption of analgesics cannot not be advised for marathon runners.

Effects on the Cardiovascular System

According to the Hannover Marathon Study data, 2.4% of the runners reported a thromboembolic disease in their past and, in light of the fact that some of them were treated with ASA as a secondary prophylaxis, it seems not surprising that 8% of runners in AG have a thromboembolic medical history vs. 1.2% in CG.

It is known that exercise can reduce the cardiovascular risk by approximately 14%, if someone is exercising regularly for 150min/week, and approximately 20%, if exercise adds up to 300min/week. A higher exercise level exceeding 10 MET (metabolic equivalents), on the other hand, results in a risk for cardiovascular events and stroke, which is twice as high as for other individuals [2,8].

Sudden cardiac death can be induced by cardiac hypertrophy or atherosclerosis of coronaries. Kim showed that the risk for cardiac death is increased for marathon runners from 0.7:100.000 to 2:100.000 [34]. Reason for cardiac death was a plaque rupture in the coronaries caused by extreme exercise, despite the fact that the median age in the runners who participated in the studies was only 46 [35].

Distribution changes of CRP and vWF, D-Dimers and Fibrinogen can cause a plaque rupture even in healthy individuals. Marathon itself takes the runner into a higher cardiovascular risk class. For this reason, Siegel recommends consumption of ASA before a marathon, but none of other NSAID because in particular ASA and Ibuprofen, but also Diclofenac, interact with one another, reducing the anticoagulatory effect of ASA [7,36,37].

Other authors also agree on higher risk level of marathon runners, but due to a rare risk of cardiac death, they do not recommend ASA as a primary prophylaxis, but certainly as a secondary one after a cardiovascular event [38-40]. Küster describes an increase of cardiovascular events after ASA consumption and therefore advises not to take ASA before a marathon run [11].

Bärtsch formulates the problem in a different manner: Given that there is a higher aggregation level for thrombocytes, participation in a marathon cannot be recommended for people over 35 years and in particular for runners with a medical history of cardiovascular or thromboembolic events [41].

ASA is further not advisable for athletes who have a cardiomyopathy with a dilatation and fibrose of the right ventricle and therefore could suffer from ventricular fibrillation. In this case, the reason for sudden cardiac death would be the Pheidiipides Syndrome and not thromboembolic event [13,14].

Effects of NSAID on Blood Coagulation

There is a thromboembolic risk caused by marathon running. The reason presumably lies within the elevated vWF, white blood cells and D-Dimers due to a prolonged fibrinolytic activity, which is caused by an inflammatory reaction due to the high blood flow [42]. The data of the Hannover Marathon Study show a substantially lower amount of side effects such as mild gastrointestinal symptoms and no significant difference between AG (3.6%) and CG (6.6%).

Hanke and coworkers could show that marathon running in itself elevates aggregability of thrombocytes in comparison to triathlon. Reason for this phenomenon could be mechanical stress for thrombocytes; in addition, the volume of the cells appears to increase due to spleen elimination of old cells and the release of new, bigger thrombocytes [15, 16].

In the Hannover Marathon Study, there was no participant with a thrombosis or embolus, however, 2.4% of the participants had a thromboembolic medical history and 3.6% in AG took the analgesic in order to prevent a thromboembolic event. 3.6% of AG had a thrombosis in their past vs. 1.3% of CG. 100% of the runners after a myocardial infarction took acetylsalicylic acid (ASA), which is strongly recommended and are therefore in AG. The Marathon study data do not support the assumption that analgesics result in increased bleeding in joints and hematoma [11]. There was no significant difference in both study populations: 0.9% in AG vs. 1.6% in CG.

Effects on Renal Function

Consumption of analgesics may lead to hyponatremia and renal failure in connection with marathon races [11,43,44].

In the Marathon study, there was no recorded case of renal failure. Even though electrolytes as a retentions parameter were not measured, severe health problems, which necessitated a medical treatment, were not reported. It can be presumed that sporadic analgesics consumption has no influence on health condition of the kidney because the missing vasodilatation caused by reduced prostaglandin has no clinical relevance. Glomerular filtration rate can be reduced but only to a mild extent, which also has no clinical relevance. The same presumably applies to hematuria, which is reported to be found in 24% of marathon runners [45,46].

Limitations

Gold standard in medical science is a double blinded randomized controlled trial. We performed a study based on data given by marathon runners on a questionnaire basis in a retrospective manner. This setup cannot give such strong information. However, for increasing robustness of the data further investigations with a larger number of participants will be required. Furthermore, it would further be of interest to take an even closer look at the aforementioned severe side effects in order to identify confounding factors, such as unrelated risks for GI bleeding and renal failure.

Conclusion:-

Only 17% of the runners took an analgesic substance before starting the Hannover Marathon 2013. In the Hannover Marathon Study, there were no significant differences between the two groups in relation to adverse events (25% AG vs. 29% CG). It appears most probable that the reason for this is that 80% of the runners who consumed analgesics took them on race day only.

Long term usage of analgesics has many potential adverse effects, e.g., an inhibition of muscle healing and a reduced protein synthesis of muscle tissue. However, for the Hannover Marathon Study, there was a significant reduction of muscle pain and swollen joints in (8% AG vs. 16% CG).

It further appears that there is an increase of peptic ulceration and GI bleeding after consumption of analgesics, statistically relevant for peptic ulceration only. Nevertheless, given that these are potentially severe adverse events, the prophylactic consumption of analgesics cannot be recommended.

Taking into account the imbalance of homeostasis, it appears advisable to take ASA as a secondary prevention following an occlusive vascular event thereby reducing the risk of myocardial infarction, stroke, and vascular death. Patients who experienced a myocardial infarction should not take part in marathons, but rather limit themselves to moderate exercising. In case they do otherwise, they should continue to take their prescribed anticoagulation medication and should be aware of potential interactions between ASA and other analgesics.

Other runners with prescribed medication should also consult their doctor before taking analgesics before a marathon, although in the Hannover Marathon Study, we could not identify an increased amount of symptoms in runners who took analgesics in combination with another medication.

	Primary Population	Analgesics Group	Control Group	p
Age [years] (MV±SD)	45±10	46±10.8	45±10.3	p=0.4
Gender	Male: 525 Female: 130	Male: 83 Female: 28	Male: 442 Female: 102	p=0.12
Weight [kg] (MV±SD)	74±11	72.6±10.5	74.7±10.4	p=0.06
Height [cm] (MV±SD)	74.5±8	177.3±8.6	178±8.1	p=0.36
Years of Training (MV±SD)	13,5±9	14±8,2	13,3±9,4	p=0,51
Marathon Training years (MV±SD)	7,5±6	8,5±6,1	7,2±6,1	p=0,05
Finished Marathons (MV±SD)	15±61	20,8±45	14,5±64	p=0,3

Table 1:- Demographic distribution of Analgesics Group and Control Group; p is accounted after T-Test; MV is the mean value and SD the standard deviation.

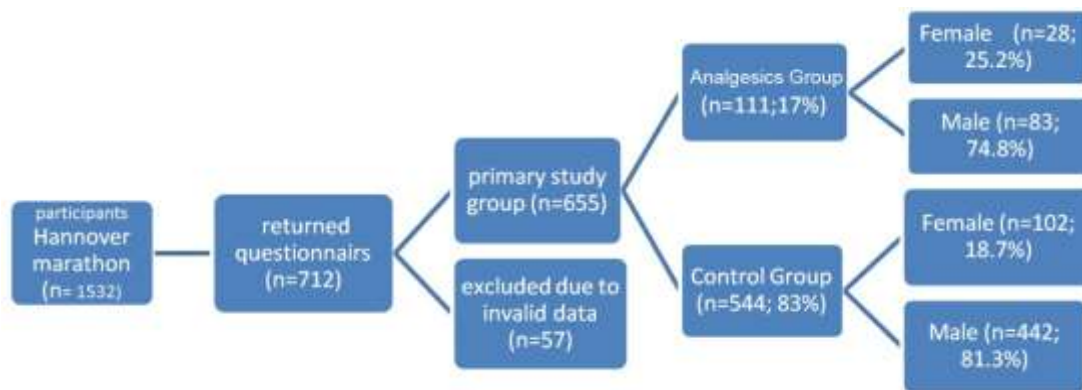


Figure 1:- Study population Hannover marathon 2013, divided into both study populations Analgesics Group and Control Group, divided into female and male groups

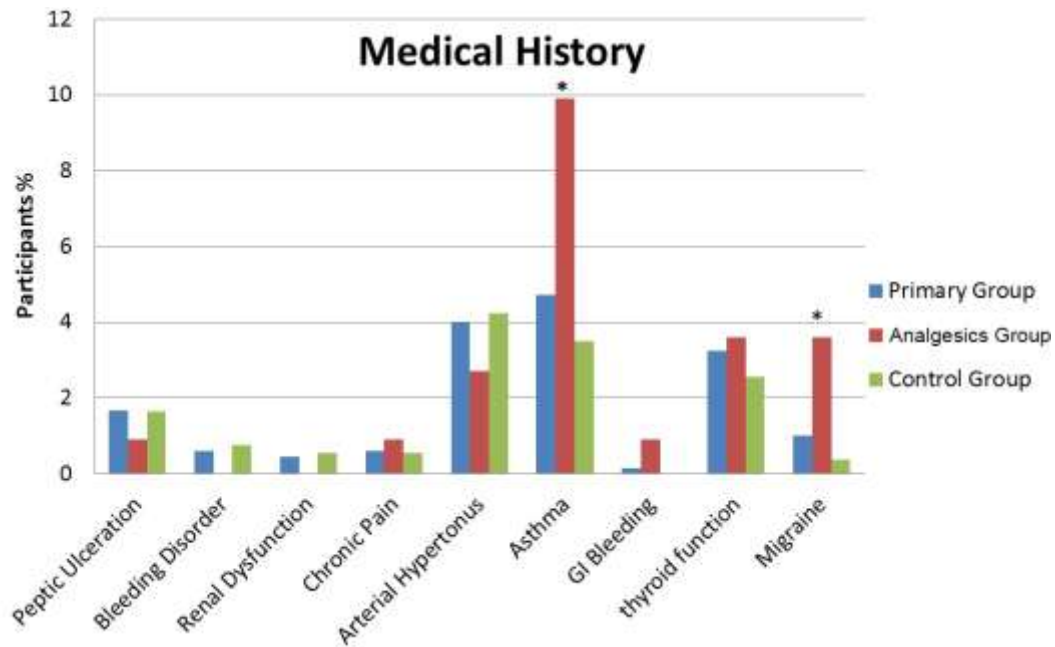


Figure 2:- Medical history of the Hannover Marathon Study population with diseases in percent, *marked are significant differences in χ^2 Test with $p < 0.05$.

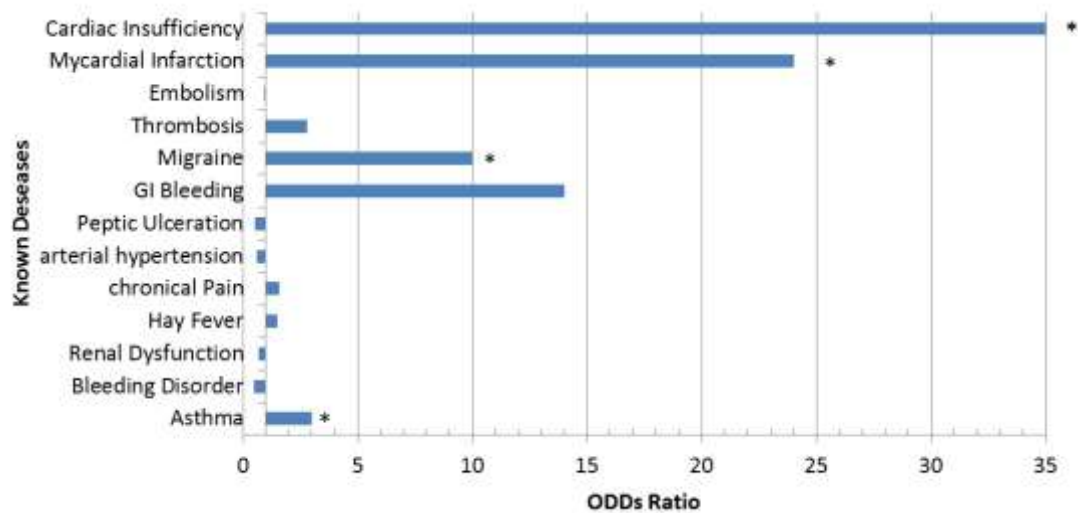


Figure 3:- ODDS Ratio of the medical history; known diseases with an ODDS Ratio higher than 1 occur more often in the Analgesics Group; if the ODDS Ratio is lower than 1, they occur one more often in the Control Group. * marked show statically significant differences in the χ^2 Test with $p < 0.05$.

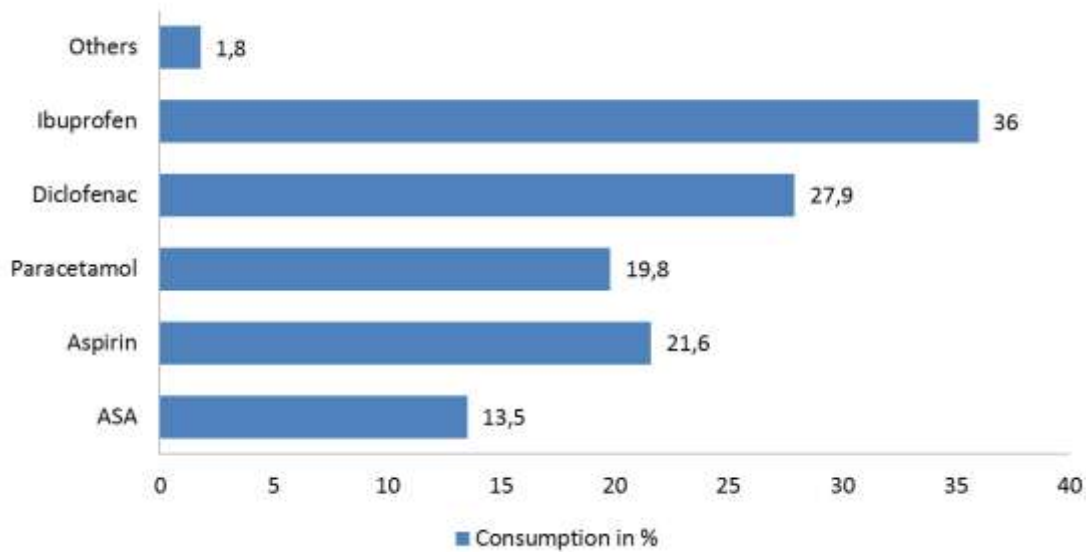


Figure 4:- Consumed analgesics in percent; as participants could name more than one analgesic, explaining numbers more than 100 in total.

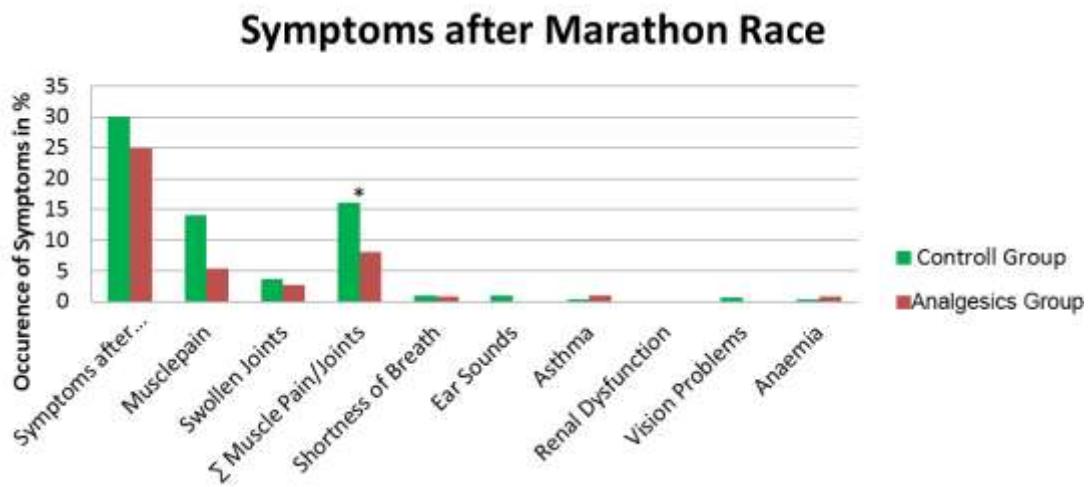


Figure 5:- Symptoms that occurred during or after the marathon in percent.

* marked show statically significant differences in the χ^2 Test with $p < 0.05$.

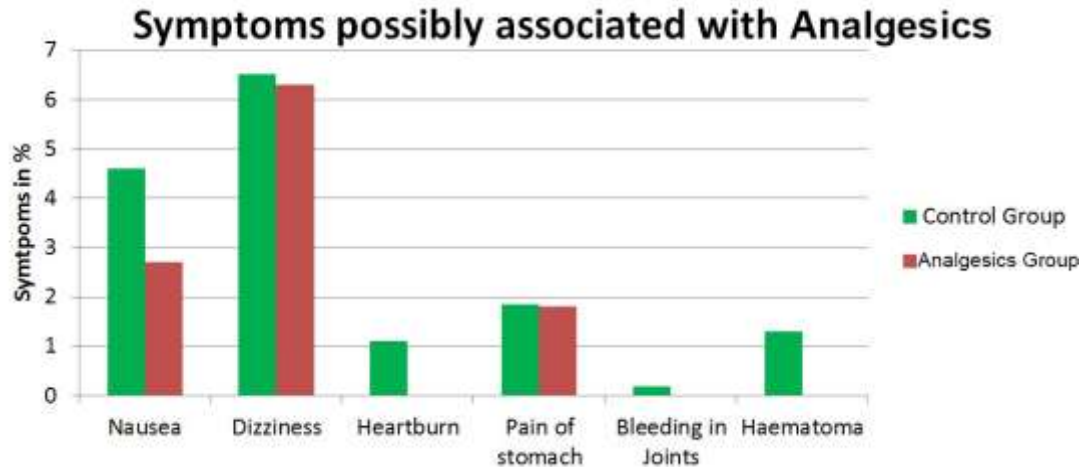


Figure 6:- Symptoms that are possibly associated with consumption of analgesics.

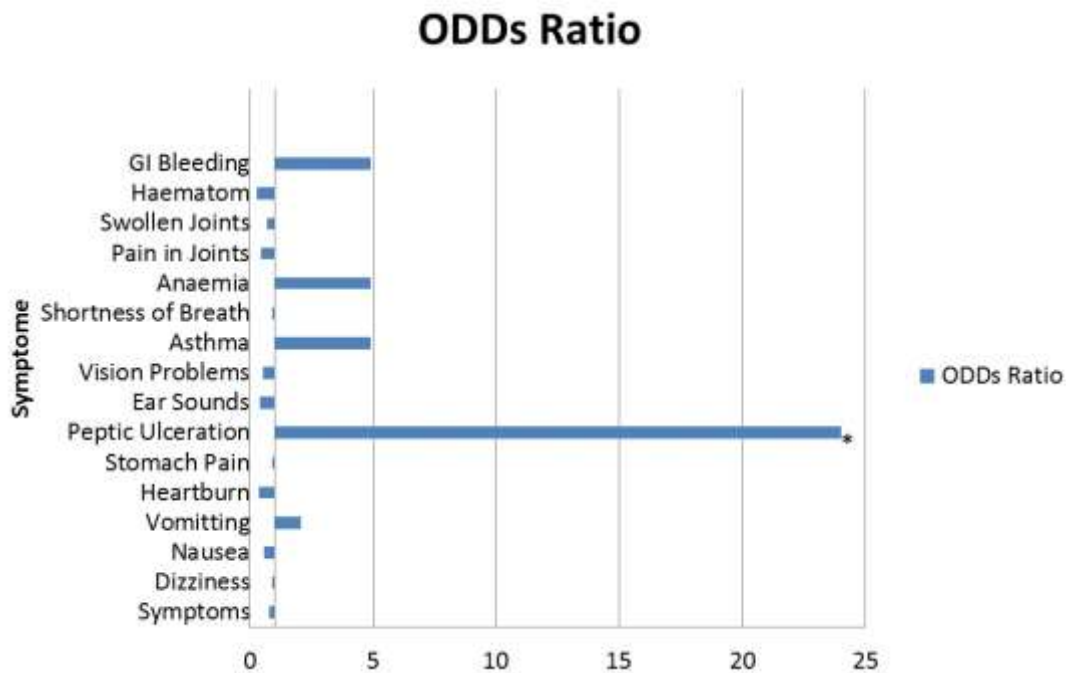


Figure 7:- ODDs Ratios for adverse events after a marathon; symptoms with an ODDs Ratio higher than 1 occur more often in the Analgesics Group; symptoms with an ODDs Ration lower than 1 occur more often in the Control Group. * marked show statically significant differences in the χ^2 Test with $p < 0.05$.

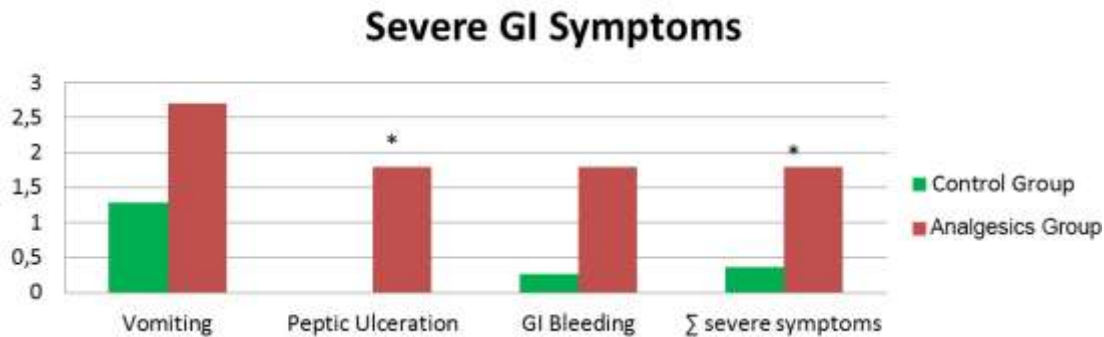


Figure 8:- Severe gastrointestinal symptoms, * marked are significant differences in χ^2 test with $p < 0.05$.

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