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Research Article

Impact of Diclofenac Sodium and N-Acetylcysteine Treatment in Patients Who are not Candidates for Varicocele Repair

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Keywords

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Abstract

Objectıves: To compare the effectivity of non-steroidal antiinflammatory and N-acetylcysteine treatment in patients with varicocele who are not candidates for varicocelectomy.

Methods: One hundred and twenty two patients (mean age of 22 years) who had grade 3 varicocele and normal testes volumes were investigated for 3 years. The patients were divided into 4 groups as 1. Control (C; n= 26), 2. NS (n=37), 3. NAC (n= 27) and 4. NSN (n=32). In group NS the patients took *diclofenac sodium* (75 mg/day, po) and in NAC the patients had *N-acetylcysteine (Nac)* (600 mg/day, po) whereas the patients in NSN took *DS* and *Nac* combination. Total sperm count (TSC), progressive motility (Spa) and slow progressive motility (Spb) were checked. The pain was evaluated by visual analogue scale (VAS).

Results: Total Sperm Concentration and Spb values were lower than initial results in group C. In NS group, Spb and VAS values declined during the study. Initial and the last TSC, Spa, Spb and VAS values were not different in NAC and NSN groups. Five patients (20%) in group C, 7 patients (19%) in group NS, 5 patients (19%) in NAC group and 4 patients (12.5%) in group NSN underwent to varicocelectomy. No adverse effect was reported in each group.

Conclusıons: NS treatment decreases pain. Combination of Nac and NS do not increase total sperm concentration. However, this combination seems to protect total sperm and progressive motile sperm concentrations by preventing harmful effects of varicocele.

INTRODUCTION

Varicocele, one treatable cause of infertility, is known as the dilatation of pampiniform plexus leading to retrograd reflux. The most accepted theories to describe the detrimental effects of varicocele are hypertermia, alterations in the testicular blood flow, renal and/or adrenal reflux, apoptosis and oxidative stress [1-6].

The degree of varicocele is described as: Grade 1 when dilated veins can only be palpated by valsalva maneuver while the patient is on erect position; Grade 2 when dialted veins can be palpated without valsalva maneuver and Grade 3 when dilated veins are visual.

N-acetylcysteine (NAC), acetylated variant of the amino acid L-cysteine, is known as the spesific antidote for acetaminophen overdose. In addition, several studies supported the other applications of NAC such as prevention of chronic obstructive pulmonary disease exacerbation, prevention of contrast induced kidney damage treatment of pulmonary fibrosis and treatment of infertility in patients with clomiphene- resistant polycystic ovary sendrome [7]. It supports the body's antioxidant and nitric oxide systems during stress, infections, toxic assault, and inflammatory conditions. Supplementation with *NAC* has been shown to increase levels of glutathione, the body's major anti-oxidant [8].

Varicocelectomy could be recommended in painful varicoceles. Some studies reported high success rates and pain resolution [9-12]. However, the first choice in painful varicocele is scrotal elevation and non steroidal anti-inflammatory drugs.

Diclofenac is a non steroidal drug and its effects on reproductive system have been reported [13,14].

In this study the patients who took conservative treatment for varicocele were observed, prospectively. We investigated the effects of diclofenac in patients with painful varicocele and NAC in painless varicocele.

METHODS

The approval of Local Ethics Committee was obtained in 2010.

One hundred and twenty two patients who had grade 3 varicocele and normal testes volumes were investigated for 3 years. All patients were informed about varicocele, risks and results (such as infertility, damage in sperm motility and morphology, pain) and the choices of treatment (conservative and surgery). All the patients in the study have read and signed the *informed approval form*.

In the first visit; duration of the pain, type of the pain, other scrotal patology or scrotal surgeries, sexual partner, number of children were inquired. The patients who did not have scrotal pain but palpable grade 3 varicocele were included into N-acetylcystein treated (NAC; n=27) group. The subjects who mentioned scrotal swelling or pain with grade 3 varicocele were randomized into non-steroidal anti inflammatory treated (NS; n=37) and non-steroidal anti inflammatory + N- acetylcystein treated (NSN; n=32) groups. Twenty six patients who had been found, accidentally, to have painless grade 3 varicocele, were randomized into control group (C; n= 26).

In control group (group C) the patients did not take any medications. In group NS, the patients took *diclofenac sodium* (75 mg/day, po) and in NAC the patients had *N-acetylcysteine* (600 mg/day, po). In NSN the patients took *diclofenac sodium* (75 mg/day, po) and *N-acetylcysteine (Nac)* (600 mg/day, po).

The patients who have undergone to varicocelectomy due to azospermia or severe oligospermia and who had a history of previous varicocelectomy were excluded to avoid bias. The degree of varicocele was evaluated by physical examination and graded as described in urological literature. Color doppler testicular ultrasound was performed to selected subjects to reveal other scrotal pathology and testis atrophy. Semen analysis was performed after three days sexual abstinences once a month. Total sperm concentration (TSC), rapidly progressive motility (SPa) and slow or sluggish motility (SPb) rates were noted. TSC was reported as million/ml. The rates for SPa and SPb were masured by computer assisted semen análisis (CASA) and calculated as percents. Pain was evaluated by 10-cm visual analogue scale (VAS). Initial results were accepted as basal values. The mean of later results were accepted as last results.

The patients were investigated prospectively for 3 years. The cases who had a TSC of 10 millions/ml and/or %SPa+SPb <40%, or severe scrotal pain persistent to conservative methods were encouraged for the surgery.

Initial and last (average) TSC, %Spa and % Spb values were compared by paired samples T test. VAS was compared by Wilcoxon test. $p < 0.05$ was accepted as statistically significant.

RESULTS

The mean age of the patients was 22 (+2, 3 SD) years.

In control group; last TSC was significantly lower than initial results (p=0.007). When we compare motility there was no difference between initial and last progressive motility. However, %Spb declined in the end of the study (p<0.001). Initial and last VAS values were not different (p=0.658) (Table 1).

In NS group, initial and last TSC were not different (p=0.11). Although %Spa showed no significant change, %Spb decreased in the end of the study (p<0.05). Decline in VAS value was statistically significant (p=0.015) (Table 2).

In group NAC, TSC did not change significantly during the study (p=0.512). Neither initial nor last results for %Spa and %Spb were different (p=0.217 and p=0.75, respectively). VAS scores did not show difference during the trial (p=0.579) (Table 3).

In NSN, TSC did not show significant changes during the study (P=0.91). There was no difference between initial and last %Spa and %Spb results (p=0.054 ve p=0.92). VAS showed no change during the trial (p=0.15) (Table 4).

Five patients (20%) in group C, 7 patients (19%) in group NS, 5 patients (19%) in NAC group and 4 patients (12,5%) in group NSN underwent to varicocelectomy (Figure 1).

Table 1: Changes in sperm parameters and VAS scores in control group during the study.

	Initial	Last	p value
Total sperm concentration (x 10^6)	50	38	**<0.007**
Progressively motile sperm (Spa) (%)	4	3	>0.05
Sluggishly motile sperm (Spb) (%)	72	52	**<0.001**
Visual analogue scale (VAS)	5.29	5.19	>0.005

Table 2: Changes in sperm parameters and VAS scores in diclofenac treated patients (NS group) during the study.

	Initial	Last	p value
Total sperm concentration (x 10^6)	44	36	0.11
Progressively motile sperm (Spa) (%)	3	3	0.11
Sluggishly motile sperm (Spb) (%)	64	57	**<0.05**
Visual analogue scale (VAS)	6.02	5.7	**<0.05**

Table 3: Changes in sperm parameters and VAS scores in N-acetylcysteine treated patients (NAC group) during the study.

	Initial	Last	p value
Total sperm concentration (x 10^6)	30	28	>0.05
Progressively motile sperm (Spa) (%)	3	2	>0.05
Sluggishly motile sperm (Spb) (%)	48	47	>0.05
Visual analogue scale (VAS)	3.7	3.8	>0.05

Table 4: Changes in sperm parameters and VAS scores in diclofenac and N- acetylcysteine treated patients (NSN group) during the study.

	Initial	Last	p value
Total sperm concentration (x 10^6)	32	31	>0.05
Progressively motile sperm (Spa) (%)	3	2	>0.05
Sluggishly motile sperm (Spb) (%)	47	46	>0.05
Visual analogue scale (VAS)	6.1	5.7	>0.05

Abbreviations: NAC: N-Acetylcysteine; NS: Non-Steroidal Anti Inflammatory Treated; NSN: Non-Steroidal Anti Inflammatory + N-Acetylcystein Treated; TSC: Total Sperm Concentration; Spa: Rapidly Progressive Motility; Spb: Slow Or Sluggish Motility; VAS: 10-Cm Visual Analogue Scale; ROS: Reactive Oxygen Species; Fors: Free Oxygen Radicals

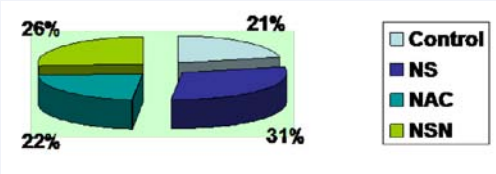

Figure 1 Five patients (20%) in group C, 7 patients (19%) in group NS, 5 patients (19%) in NAC group and 4 patients (12,5%) in group NSN underwent to varicocelectomy.

Since the subjects in the study included military staff, mostly the soldiers who did not have routine intercourse, we could not be able to state pregnancy rates properly. No adverse effect due to treatment was reported in each group.

DISCUSSIONS

Men with varicocele who have intense physical activity regularly 4–5 times a week, lasting from 2 to 4 h/day over a period of 4 years, would have risk factors for decrease in semen parameters [15] . Our subjects were all military staffs and had intense physical activity that made them to be under risk for decline in sperm parameters. This situation helped us to obtain four homogeneous groups having had the same risk for infertility/subfertiliy.

Reactive oxygen species (ROS), such as hypochlorite radical, superoxide anion and the hydroxyl radical, are highly active form of free radicals. ROS are essential for aerobic functions mostly as secondary messengers for signal transduction within cells [16]. ROS are also reported to be important in normal fertilization and play role during the acrosome and capacitation reactions by inducing hyperactivation of the sperm. ROS are rapidly cleared by the action of a host of antioxidants and excess of ROS due to an imbalance in the generation of ROS or their clearance would lead to oxidative stres [17-19].

Varicocele formation may cause astenozospermia due to free oxygen radicals (FORs) related lipid peroxidation [20]. FORs may damage sperm membrans by lipid peroxidation and also may cause defect on sperm motility. Varicoceles have been reported to be associated with an increase in the ROS generation and oxidative stress. The effects of oxidative stress are obvious in the form of abnormal morphology, motility, function, and DNA damage.

NAC is a well known antioxidant agent that may decline plasma ROS diversity. Selenium and/or N-acetyl-cysteine have been reported to induce improving semen parameters in infertile men [21]. Recently, it has been shown that men taking antioxidants (such as carnitine, vitamin E, N-acetyl cysteine, etc) had a statistically significant increase in both live birth rates and pregnancy rates [22].

There are few well-designed studies about medical treatment for varicocele. Cavallini et al. investigated the use of carnitine combined with nonsteroidal anti-inflammatory drugs for 6 months in patients with clinical varicocele and infertility and they did not achieve to solve improve in semen parameters or achieve a higher pregnancy rate [23,24]. Similar to Cavallini's study, we combined NAC and diclofenac. Differently, we observed the patients for 3 years and achieved relative improvement in semen parameters. For 3 years, TSC did not decline significantly in NAC and NSN groups, whereas the reduction was obvious in control group.

Even though the use of antioxidants to treat male infertility in patients with varicocele is considered highly controversial, recent articles have demonstrated a benefit of antioxidants in patients with varicocele [25]. Similarly, NAC seemed to have protective effect on TSC, %SPa and %SPb in the present study. Because no significant alteration was detected neither in the beginning nor in the end of the trial.

Experimental rat model studies of varicocele found an increased rate of apoptosis in the varicocele group when compared to the sham surgery group [26,27] . The apoptosis in varicocele was reported to be ROS-mediated and some authors suggested that it could be reversed through the use of antioxidants such as melatonin [28]. Although we did not investigate apopitosis, the profitable effects of NAC might be related to a function that prevented excessive apopitosis.

In our study, TSC did not show significant change in NS, NAC and NSN groups. TSC declined in control group. This may state the protective effects of NAC and diclofenac sodium. However, slow or sluggish motility (SPb) rates in NS group were lower in the end, when compared with NAC and NSN groups. This might be due to antioxidant effect of NAC. We could not appraise the pregnancy rates. This is a limitation for the study.

After we started our study; WHO and EAU revised the criteria for the nomenclature progressive motility (a),non-progressive motility (b) and non-motile sperm (c). The surgical thresholds were also revised as 40% and 32% for a+b and a. This is another limitation for our trial.

The influence of diclofenac on spermatogenesis or fertility is contradictive. Some authors concluded that diclofenac could be responsible for some cases of infertility [29]. On the other hand, Mogilner et al suggested diclofenac to be benefical for spermatogenesis following testicular ischemia-reperfusion by decreasing germ cell apoptosis [30]. In a trial, Montag et al retrieved a sufficient number of sperm by two ICSI cycles with anti-inflammatory therapy in parallel. They concluded that in cases of azoospermia and chronic genital infection, some patients would benefit from anti-inflammatory treatment prior to and during ICSI treatment [13]. Moskovitz et al observed a significant increase in sperm number and motility of spermatozoa in infertile oligo spermic men by diclofenac sodium (Voltaren) treatment [14]. In the present study, NS seemed to have had a protective impact on TSC. This finding has been supported by previous studies [13,14,30]. However, %SPb declined during the study probably due to an unknown negative effect of diclofenac on spermatogenesis as Mendonça et al. concluded, previously [29].

According to our findings, combination of NAC and NS do not increase total sperm concentration. However, this combination seems to protect total sperm concentration and progressive motile sperm concentration, probably by preventing harmful effects of varicocele related oxidative stress. NAC may play the major role in this effect. Diclofenac, but not NAC, decreases pain. Since, the combination of diclofenac with NAC may be useful in patients who have painful varicocele, but that are not candidates for varicocelectomy.

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