A COMPARISON OF DEXAMETHASONE AND METOCLOPRAMIDE FOR PREVENTING PAIN ON INJECTION OF DIAZEPAM

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Abstract- Intravenous administration of dexamethasone before diazepam injection seems to reduce the incidence of pain on injection. We conducted a randomized, prospective, double-blind, placebo-controlled clinical trial to compare effect of dexamethasone, metoclopramide and placebo in reducing the injection pain. A total of 120 ASA class I and II men aged 20-45 years that needed more than one intravenous access were enrolled in the study and were randomly allocated to one of the three groups: group 1, 2 ml intravenous normal saline and 2 ml dexamethasone (8 mg); group 2, 2 ml intravenous normal saline and 2 ml metoclopramide (10 mg), and group 3, 2 ml intravenous dexamethasone (8 mg) and 2 ml metoclopramide (10 mg). After 30 seconds, 1 ml diazepam (5 mg) was injected simultaneously into each of patients' hand veins and a maximal visual analog scale (VAS) for pain of each venous discomfort was assessed separately. In group 1, the mean of VAS for pain was significantly less in dexamethasone pretreatment than saline pretreatment. In group 2, the mean of VAS for pain was significantly less in metoclopramide pretreatment than saline pretreatment. In group 3, the mean of VAS for pain was significantly less in dexamethasone pretreatment than metoclopramide pretreatment. There were no significant differences in incidence of pain between pretreatment and placebo in three groups. Dexamethasone or metoclopramide pretreatments are effective in reducing the severity of pain on injection of diazepam and dexamethasone pretreatment has greater efficacy in reducing the intensity of pain.

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Key words: Dexamethasone, metoclopramide, pain, diazepam

INTRODUCTION

One disadvantage of diazepam is pain on injection which is sometimes very distressing to patients. Many different methods have been proposed to reduce the incidence or severity of this adverse effect, such as injection into a large vein, pretreatment with intravenous local anesthetics, opioids, metoclopramide (1) or diphenhydramine (2).

Although there are a few reports about the analgesic activity of dexametasone (3-6), there are no published studies investigating the analgesic efficacy of dexamethasone in abolishing the pain associated with diazepam injection. We observed that the intravenous injection of dexamethasone before diazepam injection seemed to reduce the incidence of pain on injection. Therefore, we conducted a randomized, prospective, double-blind, placebo-controlled clinical trial to compare effect of dexamethasone, metoclopramide and placebo in reducing the injection pain of diazepam. The aim of this study was to compare efficacy of dexamethasone with metoclopramide for the reduction and prevention of diazepam injection pain.
Dexamethasone for prevention of pain

MATERIALS AND METHODS

After the institutional review board approval and informed consents obtained, 120 ASA class I and II men aged 20-45 years, undergoing various elective surgical procedures who needed more than one intravenous access were enrolled in the study. Patients received verbal and written description of the study and gave signed informed consent before enrollment.

Exclusion criteria were a history of chronic pain syndromes, thrombophlebitis, neurological disease, analgesic administration at the time of the study and any contraindication for dexamethasone or metoclopramide administration.

Patients were randomly allocated to one of the three groups (40 patients in each group). In preoperative visits, the patients were educated and familiarized with visual analog scale (VAS) for pain (0, no pain; 10, severest pain). Sedative and analgesic premedications were not given. In the respective rooms, two 22-gauge canulas were inserted into veins on the dorsum of both hands. Then, patients in the groups received one of the three pretreatment regimens as follows:

Group 1: 2 ml intravenous normal saline into one hand and 2 ml dexamethasone (BP formula, 8 mg) into the other.

Group 2: 2 ml intravenous normal saline to one hand and 2 ml metoclopramide (BP formula, 10 mg) into the other.

Group 3: 2 ml intravenous dexamethasone (BP formula, 8 mg) into one hand and 2 ml metoclopramide (BP formula, 10 mg) into the other.

Patient's recruitment and preparation of blinded treatment syringes were done by one investigator. All injections and evaluations were done by other investigators. All test solutions were at room temperature. After 30 seconds, 1 ml (BP formula, 5 mg) diazepam was injected concurrently into each of patients' hand veins and 15-30 seconds after diazepam bolus injection, a maximal VAS for pain of each venous discomforts were assessed separately when patient experienced pain. After this, the choice of anesthetic technique was left to the discretion of the attending anesthesiologist.

Statistical analysis was performed by SPSS package (SPSS INC, Chicago OIL). Demographic data and incidences of pain were analyzed by χ² and analysis of variance tests. The intensity of pain was analyzed by two-sample t test. P value < 0.05 was considered statistically significant. The power of study was considered 20%.

RESULTS

There were no significant demographic differences between the groups (Table 1).

In group 1, the mean of VAS for pain was significantly less in dexamethasone pretreatment than saline pretreatment (P < 0.001, Fig. 1) There were no significant differences in incidence of pain (VAS > 1) between two pretreatments.

In group 2, the mean of VAS for pain was significantly less in metoclopramide pretreatment than saline pretreatment (P < 0.05, Fig. 1) There were no significant differences in incidence of pain between two pretreatments.

In group 3, the mean of VAS for pain was significantly less in dexamethasone pretreatment than metoclopramide pretreatment (P < 0.05, Fig. 1) There were no significant differences in incidence of pain between two pretreatments.

Table 1. Demographic data and ASA class of different groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=40)</th>
<th>Group 2 (n=40)</th>
<th>Group 3 (n=40)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>30 ± 2.3</td>
<td>29 ± 2.4</td>
<td>30 ± 1.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 13</td>
<td>72 ± 13</td>
<td>72 ± 12</td>
</tr>
<tr>
<td>ASA Class (HII)</td>
<td>25/15</td>
<td>28/12</td>
<td>28/12</td>
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</table>

*Data are given as mean ± SD unless specified otherwise.
†There were no significant differences between groups. Group 1, normal saline and dexamethasone; group 2, normal saline and metoclopramide; group 3, normal saline and dexamethasone.

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DISCUSSION

Our study demonstrates that both intravenous dexamethasone (8 mg, BP formula) and metoclopramide (10 mg, BP formula) significantly reduce VAS for pain score on diazepam injection compared with saline. We found that intravenous dexamethasone pretreatment had a greater efficacy in reducing the intensity of pain. Because we compared treatment and placebo in the same subject, probably we could nearly eliminate all of the confounding factors.

As noted earlier, various strategies have been investigated to reduce the incidence and severity of diazepam injection pain. Majed et al. reported that in comparison with placebo, pretreatment with lidocaine or metoclopramide before diazepam injection reduced the intensity and incidence of pain, and lidocaine pretreatment was more effective (1). In our study, although metoclopramide pretreatment reduced the intensity of pain significantly, there were no differences between the incidence of pain with metoclopramide and saline pretreatments.

Metoclopramide was first developed as a structural analogue of procainamide and is relatively devoid of local anesthetic and antiarrhythmic activity. Although metoclopramide, like morphine, may alter the influx of calcium ions across the membrane to produce a generalized analgesic effect, the exact mechanism whereby it prevents local pain is unknown (7). We chose metoclopramide to test its efficacy to reduce pain on diazepam injection again and with a different method that can be more accurate. Dexamethasone, a corticosteroid with strong anti-inflammatory effects, prevents nausea and vomiting in patients undergoing chemotherapy (8) and reduces postoperative nausea and vomiting (9). A few studies have demonstrated the analgesic effect of corticosteroids (3-6). Mirzaei et al. reported that the combination of corticosteroids and bupivacaine diminishes postoperative back pain experienced by patients undergoing lumbar disectomy in the immediate postoperative period (3).

Corticosteroids also have been studied for postoperative pain relief in oral surgery. Skjetnløth and Loken found that 9 mg of betamethasone after dental surgery alleviated postoperative pain and swelling effectively (5). Although analgesic effects have been reported after general surgery and orthopedic surgery (5) other studies have not corroborated these reports (10, 11). For the first time, we report that dexamethasone pretreatment can reduce intensity of the pain on injection of diazepam. The mechanism of
Dexamethasone for prevention of pain

dexamethasone–induced analgesia is not fully understood, but with its strong anti-inflammatory effect, dexamethasone theoretically is beneficial for acute surgical pain. However, it is doubtful that anti-inflammatory effect of dexamethasone accounted for its analgesic effect in the current study because of its delayed onset of action.

The studies on pain usually accompany with the problem of quantifying the sense of pain. Between the methods of pain quantification, VAS for pain is usually used. Nevertheless, applying VAS for pain also has some problems. According to the pain threshold and the way pain is to be exhibited in different people, VAS can not be very accurate and can confound the results of the studies. In order to overcome this problem, for the first time, we used both hands of the patients, one serving as a case and the other as a control. We think we can rule out many of the confounders with this method.

In conclusion, we have shown that dexamethasone or metoclopramide pretreatments are effective in reducing the severity of pain on injection of diazepam and also, dexamethasone pretreatment has greater efficacy in reducing the intensity of pain. The use of dexamethasone is an acceptable alternative to other strategies of pain control when an anti-emetic agent or a corticosteroid is to be administered as part of the anesthetic technique.

REFERENCES


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Abstract- It seems that incidence and variety of the known sexually transmitted diseases (STDs) in our country have changed in recent years. We performed this study to evaluate these changes. A total of 56 male patients who had clinical symptoms of urethritis were evaluated. Also the relationship between urethritis and factors such as age, occupation, marital status, source and place of infection, and arbitrary consumption of antibiotics and results of susceptibility test for antibiotics against Neisseria gonorrhoeae were examined. The final results of the evaluation were compared with the similar results of previous evaluation which was done 8 years ago among the same number of patients. In the recent study, 55.3% of infected people were in 21-30 age group. The source of infection in 11 cases (19.64%) was from foreign countries and in 45 cases (80.35%) it was from within the country. In 75% of cases (24 cases) urethritis was gonococcal (GU) and 25% (8 cases) were non-gonococcal urethritis (NGU). In GU, Spectinomycin, ciprofloxacin, erythromycin and doxycyclin were effective in 100% of cases and Co-Trimoxazol (sulfamethoxazole-trimethoprim), tetracyclin, penicillin and ampicillin were effective in 50%, 33.3%, 23.5% and 16.6% of cases in vitro, respectively. In the evaluation 8 years ago, 64.58% (31 cases) were among 21-30 age group. In 13 cases (41%) the source of infection was from foreign countries and in 19 cases (59%) was from within of country; 85% (41 cases) were GU and 15% (7 cases) were NGU.


Key words: Urethritis, gonococcal, nongonococcal

INTRODUCTION

Urethritis in men is divided in to two main groups of gonococcal urethritis (GU) and non-gonococcal urethritis (NGU). GU is associated with the gram-negative diplococcus called Neisseria gonorrhoeae but NGU is a syndrome with several causes; two important and potentially dangerous pathogens involved in it are Chlamydia trachomatis and Ureaplasma urealyticum (1, 2). The incubation period for GU varies from 3 to 10 days. The usual incubation period for NGU is 1 to 5 weeks. Symptoms and signs are urethral discharge, burning on urination, meatal edema and erythema and urethral itching. In GU, the discharge is profuse and purulent but in NGU the discharge is more scant and cleaner than in GU.

In both GU and NGU, the specimens must be collected with a calcium alginate (Calgizwab Inlox) urethrogenital swab, waiting at least one hour, preferably 4 hours, after the patient has urinated before swabbing. Swabs must be inserted 2 to 4 cm into the urethra. Specimens must be obtained from within urethra in the morning and not simply from a drop of discharge. Trained laboratory personnel who regularly read Gram’s stains can make the diagnosis of gonorrhea with approximately 95% sensitivity and 99% specificity. Diagnosis of NGU requires demonstration of urethritis and exclusion of infection with N. gonorrhoeae. On Gram stain of a urethral swab the presence of more than four polymorphonuclear leukocytes per oil-immersion field confirms NGU (3).
Comparative analysis of urethritis

Although in recent past GU could successfully be treated with penicillin, the gonococcus has acquired a plasmid for penicillinase production, making some strains totally resistant to penicillin, ampicillin and tetracycline (penicillinase-producing N. gonorrhoeae). Center for Disease Control and Prevention has issued recommendations for using antibiotics like ceftriaxone, cefixime, ciprofloxacin, ceftriaxone and spectinomycin. Since about 30% of men with GU are also infected with C. trachomatis these antibiotics must be used along with tetracycline or its derivatives.

The personal tendency of patient with sexually transmitted diseases (STDs) to refer to private clinics was the reason to do a study about characteristics of urethritis in a private clinic and to compare the results with a similar study performed 8 years ago.

MATERIALS AND METHODS

In this study we evaluated 56 males in private clinic from September 1999 to November 2000 who came to the clinic with symptoms of urethritis. Factors such as age, occupation, marital status, source and place of infection, record of taking antibiotics before clinical examination, results of laboratory assessment, culture and antibiogram all were evaluated. Specimens were collected from morning discharge. Diagnosis of GU was on the basis of the evidence of Gram negative diplococcus in intracellular and extracellular in Gram’s staining and clinical symptoms of urethritis and for NGU seeing more than four polymorphonuclear leukocytes per field in five 1000-power oil-immersion fields and no evidence of Gram negative diplococcus in specimens (3). In the recent study (1999-2000) detection of Chlamydia infection was was performed by direct fluorescent antibody testing (DFA) in all the patients.

We prescribed synchonic spectinomycin, 2 gr, intramuscularly as a single dose and doxycycline 100 mg twice a day for 7 days for all patients, including 22 patients who had taken antibiotics arbitrarily before coming to the clinic. We followed these patients for detecting complications.

The final results were compared with the results of a similar study with the same number of patients 8 years ago (from July 1990 to March 1993).

RESULTS

Figure 1 shows age distribution of patients. The youngest patient was 18 years old and the oldest one was 48. Most of the infected people were 21-30 years of age.

In the study performed from 1990 to 1993, 85% of cases were GU and 15% were NGU; 47% of patients were single and 53% were married. In recent study (1999-2000), 75% of cases were GU and 25% were NGU, and 53.3% of patients were single and 44.6% were married. Comparison of two groups showed an increase in NGU and an increase of the disease among the single people ($P = 0.016$ and $P = 0.3$, respectively).

Table 1 shows the relation of diseases frequency with the occupation of the patients. In the present study among the different jobs, shopkeepers and businessman had the highest rate of 44.64%. In the previous study (1990-1993) the highest rate was among the drivers and shopkeepers (24% for each of them) but in the present study the drivers formed only 7.4% of the patients.

In the previous study source of infection was from foreign countries in 41% of cases and from inside Iran in 59%, but in the recent study in 19.64% (11 cases) source of infection was from foreign countries and in 80.35% (45 cases) from inside Iran.

Figure 2 shows results of antibiogram efficiency of antibiotics against N. gonorrhoeae.

All of our patients were cured. In the long-term follow up of the patients in the recent study (1999-2000), no complications like epididymitis, prostatitis and urethral syndrome were seen.

![Fig. 1. Age distribution of patients.](image)
DISCUSSION

The incidence and variety of the STDs have greatly increased since the 1970s. In addition to the five classic venereal diseases (syphilis, gonorrhea, chancroid, granuloma inguinale and lymphogranuloma venerum), genital herpes infection, genital warts and AIDS are increasing rapidly among sexually active people. Although the incidence of GU has been decreased since 1986 but GU and NGU are still very prevalent diseases (1). Because of cultural and religious beliefs, prevalence of venereal diseases is low in our country but since the infected partners are unavailable and they are distributed widely in the society, venereal diseases are still recognized as a serious danger.

In 1999, Brackbill and colleagues showed that in United States half of infected people with STD had gone to private clinics (49%) and only 5% of these people had gone to STD clinics and were treated there (4).

In our previous study (1990-1993), source of infection in 41% of cases was from outside of country and the remaining 51% were from inside, but in our recent study (1999-2000) this figures changed to 19.64% and 80.35, respectively. These changes show that in recent years the availability to the infected partners as the source of infection was easier and because of their low level of hygienic patterns and incorrect treatment, prevalence of venereal diseases has been increased ($P = 0.03$). However, other factors including decrease in overseas travels may affect the results. In the previously studied figures, two groups of occupations, i.e. shopkeepers and drivers, each of which with 24% were showing the highest rate of urethritis, but in the recent one, the shopkeepers with 44.64% (25 cases) had the highest rate and drivers consisted only 7.14% (4 cases) among the total of 56 cases, an increase among the shopkeepers was considerable. Comparison of two studies shows an increase of NGU and increase of the disease among the single people ($P = 0.016$ and $P = 0.3$, respectively). In recent study (1999-2000) in all of patients for detection of Chlamydia infection direct fluorescent antibody testing (DFA) has done and in 21 cases test was positive that indicated the high prevalence of Chlamydia infection in patients with

Table 1. The relation of diseases frequency with occupation 1999-2000

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<tr>
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<tbody>
<tr>
<td>Shopkeeper</td>
<td>25 (44.64%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Service sector</td>
<td>10 (17.85%)</td>
<td></td>
</tr>
<tr>
<td>Worker</td>
<td>7 (12.5%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Employee</td>
<td>7 (12.5%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Driver</td>
<td>4 (7.14%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Student</td>
<td>3 (5.35%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Misc.(Peasant, Unemployed and soldier)</td>
<td>4 (9%)</td>
<td></td>
</tr>
</tbody>
</table>
Comparative analysis of urethritis

gonococcal and nongonococcal urethritis. Highest rate of infectious people was among the age group of 21-30, but in the previous study it was 64.58% and in recent one it was 55.3%, which justifies considering high level of sexual activities in this age group. Dallabetta and colleagues concluded in their study that the high prevalence of asymptomatic infection at follow up in a population of men who received suboptimal antimicrobial therapy suggests that the most effective therapy available should be given at the first visit (5). Djajakusuma and colleagues from Indonesia showed that among 107 male patients with a complaint of urethral discharge who were followed up, 104 (97%) were clinically cured initially with ciprofloxacin 500 mg single oral dose plus doxycycline 100mg, twice daily for 7 days. From economic point of view, the cost of initial treatment of each patient was SUS 2.56 and the cost of microbiological diagnosis and treatment each was SUS 18.70. So they recommended the initial treatment for patients with symptoms of urethritis without any laboratory examinations (6). Schwebeke and colleagues from Mongolia have reported that among 260 male patients with GU, 42% of isolated N. gonorrhoeae had plasmid mediated resistance to penicillin and chromosomal resistance to penicillin, tetracycline, and ciprofloxacin (7). As figure 2 shows, the presence of penicillinase producing varieties of N. gonorrhoeae in our society cause that antibiotics such as penicillin, ampicillin, sulfamethoxasol-trimetoprim and tetracycline are not effective against this microorganism in all cases; on the contrary, antibiotics such as ceftizoxime, spectinomycin, ciprofloxacin and doxycycline are very effective on N. gonorrhoeae in vitro. How much do the results obtained from in vitro tests correspond with the clinical results (in vivo) is controversial. In the recent study, 22 patients had taken antibiotics arbitrarily before coming to the clinic. The symptoms among them had been reduced or the form of disease had been changed from gonococcal to nongonococcal (Post gonococcal urethritis). They had acted as the bearer of microorganism and had disseminated the disease.

In this study, 100% of our patients were cured with synchroic spectinomycin, 2 gr. intramuscularly as a single dose and doxycycline 100 mg twice a day for 7 days. To prevent the chronic complications of gonococcal and nongonococcal urethritis like epididymitis, prostatitis and urethral syndrome, 22 patients who had taken antibiotics arbitrarily before coming to the clinic were prescribed the above therapeutic protocol in their first visit like other patients. In the long-term follow up of the patients in the recent study (1999-2000), no complications like epididymitis, prostatitis and urethral syndrome were seen.

REFERENCES


