Eur J Pediatr (1987) 146 [Suppl 2]: S56–S58

European Journal of
Pediatrics

Treatment of cryptorchidism with low doses of buserelin over a 6-months period

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Abstract. In a collaborative study, 48 prepubertal boys with undescended testes ranging in age from 15 months to 11 years were treated with low-dose intranasal buserelin following an every-other-day programme for a period of 6 months. Urinary LH, FSH, and testosterone were not altered during the treatment period. Boys over 7 years of age experienced a slight but significant rise in testosterone at the end of treatment. Testicular descent was achieved in only 17% of boys. In the remainder, bilateral testicular biopsies were obtained during orchiopexy. Grouped analysis showed a significant increase in the number of germ cells per tubule in both unilateral and bilateral cryptorchid boys, suggesting that buserelin treatment of the testis in a cryptorchid position is capable of improving fertility potential. If time-matched controls are compared to treated boys of the same age, again a significant difference is observed indicating that buserelin treatment does increase the germ cell count.

Key words: Undescended testes – Intranasal buserelin – Testicular descent – Fertility

Introduction

A decreased sperm count and consequent increased risk of infertility is seen in a significant percentage of patients with a history of undescended testis [9]. If the germ cell count was less than 0.1 per tubule, surgery performed before puberty fails to restore normal fertility [3]. When a low dose of buserelin (GNRH analogue) is used for a period of 6 months following successful surgery for cryptorchidism, it is possible to stimulate germ cell division in boys with both unilateral or bilateral cryptorchidism [4]. Native GNRH (Cryptokur) has been shown to induce testicular descent in about 50% of boys treated [5]. This collaborative study was undertaken to find out whether buserelin (GNRH analogue) given over a 6-month period would induce testicular descent and at the same time increase the germ cell count in the testes of cryptorchid boys.

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Patients and methods

Ten micrograms of buserelin was given as a nasal spray every other day for 6 months to 39 boys with unilateral cryptorchidism and nine boys with bilateral cryptorchidism. This study group comprised patients from Basel (23 unilateral and four bilateral) and Philadelphia (16 unilateral and five bilateral). The endocrine effects of buserelin were determined in the Philadelphia group by studying the first morning void 12 h after buserelin administration and in the Basel group by studying a urine specimen collected 36 h after the last buserelin administration. These determinations were performed every 30 days. LH, FSH, and testosterone were determined by radioimmunoassay and expressed as international units per gram creatinine. After 6 months of treatment, if the testis remained undescended, the boy underwent orchiopexy. At the time of surgery, a small testis biopsy provided tissue for light- and electron-microscopic examination. Thirty-two unilateral testes and 14 bilateral testes were biopsied. Testis biopsies were fixed in 3% cold gluteraldehyde, postfixed in 1% OsO_4 and embedded in Epon as previously described by Hadziselimovic. Testis biopsies were examined blindly by one pathologist in Philadelphia independently at 50× magnification. In five treated patients where the germ cell count varied considerably, a re-examination was performed on Basel slides by pathologists from Philadelphia to ensure that the difference was not due to technical factors. The results were compared to the original findings from Basel, and no significant differences in the counted number of germ cells were found between two observers. A cross-section of at least 50 tubules per biopsy was examined in order to provide an average number of germ cells per tubule. Testis biopsies from 99 prepubertal unilateral cryptorchid boys (42 Philadelphia, 57 Basel) and 48 prepubertal bilateral cryptorchid boys (14 Philadelphia, 32 Basel), aged 13 months to 11 years, formed a control group. Statistical analysis was carried out using the Wilcoxon-Mann-Whitney U test.

Results

Successful descent of the testis was induced in only 17% of boys. All eight testes which descended – seven unilateral and

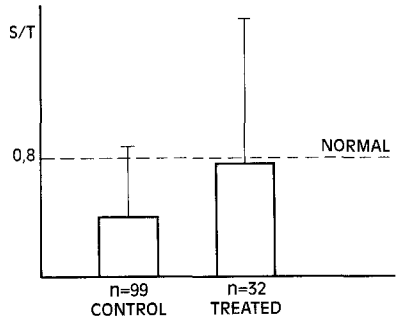

Fig. 1. Germ cell number per tubular cross-section *(S/T)* in untreated and buserelin-treated unilateral cryptorchid boys. Significant increase in the number of germ cells was achieved after treatment ($P < 0.008$)

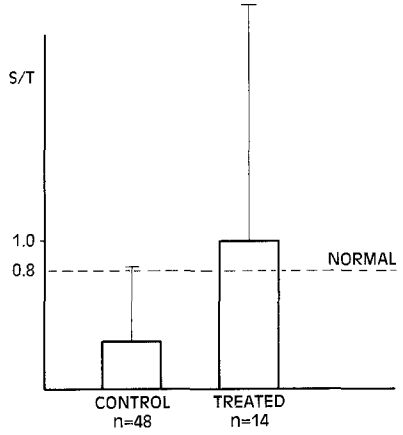

Fig. 2. Germ cell number per tubular cross-section *(S/T)* in control and buserelin-treated bilateral cryptorchid boys. A significant increase was obtained in the treated group ($P < 0.007$)

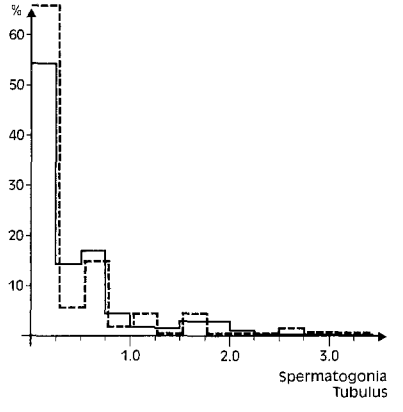

Fig. 3. Histogram of the germ cell number per tubular cross-section in unilateral and bilateral cryptorchidism. Bilateral cryptorchid patients *(broken line)* have a higher proportion of biopsies completely lacking germ cells and a lower proportion with 0.25–0.5 germ cells per tubule

one bilateral – were located prescrotally prior to beginning treatment. All remained in a satisfactory scrotal position after the end of treatment.

In boys with unilateral undescended testis who were treated with 6 months of low-dose buserelin, the mean number of germ cells per tubule after treatment was 0.77 ± 0.97, compared to 0.39 ± 0.49 germ cells per tubule seen in the untreated control group (Fig. 1). This difference is statistically significant ($P < 0.008$). In the boys with bilateral undescended testes who were treated, the germ cell count was 1.02 ± 1.6 germ cells per tubule compared to 0.32 ± 0.5 germ cells per tubule in bilaterally cryptorchid untreated boys (Fig. 2). This difference is again statistically significant ($P < 0.007$). Biopsies from untreated boys with unilateral cryptorchidism were also compared with biopsies from boys with bilateral cryptorchidism (Fig. 3), and observed that the germ cell count in bilateral cryptorchidism was significantly lower ($P < 0.009$).It was noted that the bilaterally cryptorchid boys had more testes with no germ cells and fewer biopsies in which the germ cell count was from 0.25 to 0.5.

Endocrine studies showed that LH, FSH, and testosterone all remained unchanged both 12 h and 36 h after buserelin administration throughout the study [7]. In boys over 7 years of age, there was a low but significant increase in urinary testosterone at the completion of treatment in comparison to younger boys [7].

Discussion

The LH-RH analogue buserelin appears to be about ten times more active than native LH-RH. It has been shown to cause an increase in germ cells per tubule if administered following successful orchiopexy in boys with an initial low germ cell count [4]. This study has suggested that it may be possible to increase the number of germ cells by means of hormonal treatment given with the testis in an undescended position. This may give additional support to the hypothesis that the low germ cell count of cryptorchid boys is caused by an impaired hypothalamo-pituitary-gonadal axis, a forme fruste of hypogonadotropic hypogonadism [2, 6]. It does not appear that the germ cell counts are depressed solely on the basis of elevated temperature or pressure, as has been generally believed. In this study, no side effects were noted. Especially to be noted was the lack of evidence of down-regulation of the hypothalamo-pituitary-gonadal axis during the study. The fact that boys over 7 years of age showed a low but significant increase in testosterone indicates an indirect stimulatory effect of buserelin on Leydig cells. We could not demonstrate this effect on urinary testosterone in young cryptorchid boys in spite of an observed increase in Leydig cell number, suggesting an increase in intratesticular testosterone [4].

Buserelin was significantly less effective in inducing the descent of an undescended testis than native LH-RH alone or native LH-RH and hCG [1, 5, 8]. Thus, buserelin is not a drug of choice to induce testicular descent.

It has been demonstrated that between 6 months and 2 years of age there is a progressive decrease in germ cells per tubule (this issue). Additionally, the higher the location of an undescended testis, the lower is the germ cell count per tubule. Accordingly, in order to critically analyse the effects of buserelin, it is important to control for both age and position. On analysing the Philadelphia data from the control group (not treated), a significant increase in the number of germ cells in cryptorchid boys over the period of observation of 1.5 years was noted. Therefore time-matched 1- to 6-year-old controls are compared to 1- to 6-year-old cryptorchid boys treated with buserelin, and a significant difference is observed (controls ($n = 13$) $\bar{x} = 0.24 \pm 0.41$, treated ($n = 25$) $\bar{x} = 0.85 \pm 1.1$ germ cell per tubule; $P = 0.0038$). No difference was found in germ cell count between Philadelphia and Basel treated groups (Philadelphia $\bar{x} = 0.66 \pm 0.87$, Basel $\bar{x} = 1.1 \pm 1.3$).

References

1. Hadziselimovic F (1986) Hormonal treatment of cryptorchidism. N Engl J Med [Letter] 315:322
2. Hadziselimovic F, Girard J, Herzog B (1978) Lack of germ cells and endocrinology in cryptorchid boys from one to six years of life. In: Bierich JR, Giarola A (eds) Cryptorchidism. Academic Press, New York London
3. Hadziselimovic F, Hecker E, Herzog B (1984) The value of testicular biopsy in cryptorchidism. Urol Res 12:171–174
4. Hadziselimovic F, Hoecht B, Herzog B, Girard J (1984) Does long-term treatment with Buserelin improve the fertility chances of cryptorchid testes? In: Labrie F, Belanger A, Dupont A (eds) LHRH and its analogues. Elsevier, Amsterdam
5. Hadziselimovic F, Girard J, Herzog B (1984) 4 Jahre Erfahrung mit der hormonellen kombinierten Behandlung des Kryptorchismus. Z Kinderchir 39:324–327
6. Hadziselimovic F, Thommen L, Girard J, Herzog B (1986) The significance of postnatal gonadotropin surge for testicular development in normal and cryptorchid testes. J Urol 136:274–276
7. Hadziselimovic F, Huff D, Duckett J, Herzog B, Elder J, Snyder H, Buser M (1987) Long-term effect of LHRH-analogue (Buserelin) on cryptorchid testes. J Urol (in press)
8. Höcht B (1979) Klinische Erfahrungen mit der LHRH Behandlung beim präpubertalen Maldescensus testis. Habilitationsschrift, Universität Würzburg
9. Kogan JS (1983) Fertility in cryptorchidism. In: Hadziselimovic F (ed) Cryptorchidism: management and treatment. Springer, Berlin Heidelberg New York, pp 71–82