Meta-Analysis

The effect of leuprolide acetate treatment on luteinizing hormone suppression in children with central precocious puberty: A systematic review and meta-analysis

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ABSTRACT

Background: *Central precocious puberty* (CPP) is a characteristic development of sexual puberty as a consequence of premature activity of hypothalamic-pituitary-gonadal axis (HPG axis) before eight years old for girls or nine years old for boys. Several studies have showed different results in Leuprolide Acetate (LA) therapy for CPP in terms of administration doses and time of treatment on suppression of gonadotropine secretion.

Objective: To determine the effects of different administration of LA therapy, monthly doses, and every three months doses on suppression of LH secretion in CPP patients.

Method: This study is a meta-analysis of systematic reviews available from Cochrane library, MEDLINE, EBSCO, PROQUEST and other registered reference about therapy to suppress LH secretion in CPP patients. Three researches independently conducted reviews on abstract and full-texts for inclusion criteria and data extraction, respectively.

Result: Two studies fulfilled the inclusion criteria and were included in the meta-analysis. The meta-analysis showed that LH suppression varied with different administration doses and time. These studies compared LA therapy using 11.25 mg/3 months with control 7.5 mg/month, 22.5 mg/3 months with control 7.5 mg/month, and 22.5 mg/3 months with control 11.25 mg/3 months doses.

Conclusion: The dose of LA therapy 7.5 mg/month gave greater LH suppression compared to 11.25 mg/3 months and 22.5 mg/3 months; while LA therapy 22.5 mg/3 months provided greater suppression compared to 11.25 mg/3 months. There was no difference in growth velocity with different doses of LA therapy.

Introduction

Central precocious puberty (CPP) is the development of sex pubertal characteristics as a consequence of premature activation of the hypothalamic-pituitary-gonadal axis (HPG axis) before the age of eight years in girls and nine years in boys. Pathogenesis of CPP include early activation of the release of gonadotropin-releasing hormone (GnRH), leading to increased gonadal steroid and gonadotropin secretion. The prevalence of CPP is estimated to be around 1 : 5,000 to 1 : 10,000. Central precocious puberty is more often found in girls than boys (ratio > 20 : 1).[1,2] Approximately 95% of CPP occurs in girls, and 90% of CPP in girls is idiopathic. Children with CPP may experience various growth, development, and psycho-social problems.[3] The aim of CPP management includes hormonal suppression, regression or cessation of the development of pubertal characteristics, preventing early menarche short stature in adulthood. Patients with CPP is at risk of having short stature in adulthood due to imbalance of skeletal maturation associated with growth acceleration during early epiphyseal fusion, which prevents growth.[4-7]

Gonadotropin-releasing hormone analogue (GnRHa) has become the standard care for children with CPP for more than 20 years since 1989 and is now used to inhibit pubertal progression and increase height prospect. The GnRHa preparations are available in forms of depots, such as depot leuprolide (DL) which is one treatment option for CPP available for intramuscular (IM) or subcutaneous (SC) injections.[4,8,9] It has been reported that GnRHa is safe, effective and has reversible effects on the HPG axis function. Several previous reports had shown improvement in final height with GnRHa therapy.[8]

Leuprolide acetate (LA) dose varies from one country to another, ranging from 3.75 to 15 mg with 4 weeks interval or more frequent. In the United States, the recommended initial dose is 0.3 mg/kg ranging from 7.5-15 mg. In Asia and Europe, the standard dose is 3.75 mg, while the minimum suppression dose is 0.03 mg/kg, about 1/10 of the recommended dose in the US. The initial dose in Europe and Asia tends to be lower because researchers from Japan and France have reported the achieved long-term pubertal suppression in CPP with the dose of 3.75 mg every four weeks. Badaru (2006) studied the effectivity of low dose LA 3.75 mg/month and 1.25 mg/3 months compared to 7.5 mg/month using a monthly serial comparison. [7,9-11]

The objective of this study is to compare the effect of LA treatment on luteinizing hormone (LH) secretion in CPP patients when given for one month and three months.

Methods

Selection criteria and research strategy

A systematic literature research was conducted to identify studies which fitted the criteria, written in English and without restricting the publication year. Sources used in this research were MEDLINE (Pubmed), The Cochrane Library, EBSCO, and Proquest. The investigators were contacted to obtain further study data information.

Clinical trial reports, reviews, meta-analyses, guidelines, and health technology assessment which met the inclusion criteria were included in this study. Handsearch was done for conference abstracts associated with this meta-analysis. Clinical trial registries, including WHO international registry platform and clinicaltrials.gov were searched for ongoing clinical trials.

Three investigators (RDA, ABP, KH) independently reviewed all potentially relevant articles. The investigators evaluated the title and abstract of the studies, and then the complete article. Disagreement among the three investigators was discussed to reach a consensus. Study selection flow was conducted based on modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMA). [12]

Inclusion criteria were published and unpublished *randomized controlled trials* (RCTs), girls and boys below eight and nine years old,

respectively, who presented signs of secondary pubertal signs (pubertal status ≥ Tanner 2), laboratory results showed an increase in basal LH, or LH more than 5 IU/L after GnRHa stimulation test. Subjects in the studies had to be treated with LA for at least 12 months, given monthly or every three months to evaluate suppression effect of gonadotropin secretion in the previously randomized CPP patients. LA dose was the restriction criterion in this study.

Data Extraction

Three investigators (RDA, ABP, KH) performed data extraction independently and discussed to reach a consensus on any disagreements. Data extraction included study type, research subjects, intervention, as well as the primary and secondary outcomes.

The investigators independently evaluated every study regarding bias risks, which included assessment of randomization, allocation concealment, blinding, outcome assessment adequacy, selective reporting, and other sources of biases.

Primary (LH supression) and secondary outcomes (growth velocity) were evaluated based on the mean difference, with Confident Interval (CI) 95%. When data analysis using intention-to-treat was not possible, data analysis was performed per protocol or using available data.

The authors of the analysed studies were contacted for missing data. This systematic review presented the event of drop-out, loss to follow-up, withdrawals and critically evaluated the event of these missing data. Bias assessment was not reported in the form of funnel plot because only two studies met the outcome criteria. Language and location were reporting biases in this meta-analysis because only journals in English were included and only a few databases were included.

Data Analysis

The studies analyzed were homogenous, intrastudies variability used was based on opportunities or chance. Therefore, fixed-effect model analysis was used, where only studies with a low degree of heterogeneity were analyzed.[13] In this meta-analysis, subgroup analysis could not be performed because of the data limitations. Results analysis was performed by comparing fixed-effect and random effect models. Results from the two statistic models were not different; therefore studies with fewer subjects did not affect the results.

Results

Study description

A total of 66 researches or studies were identified. After abstract screenings, 56 studies were excluded. The remaining 10 studies were included for further analysis in accordance to the agreement between the three investigators based on the full-text screening. Evaluation included congruity with the protocol's inclusion and exclusion criteria. Eight out of 10 studies which did not meet the inclusion criteria were excluded: one prospective study and two RCTs in which LA was given every three months while in other studies LA was given monthly with the dose based on body weight.

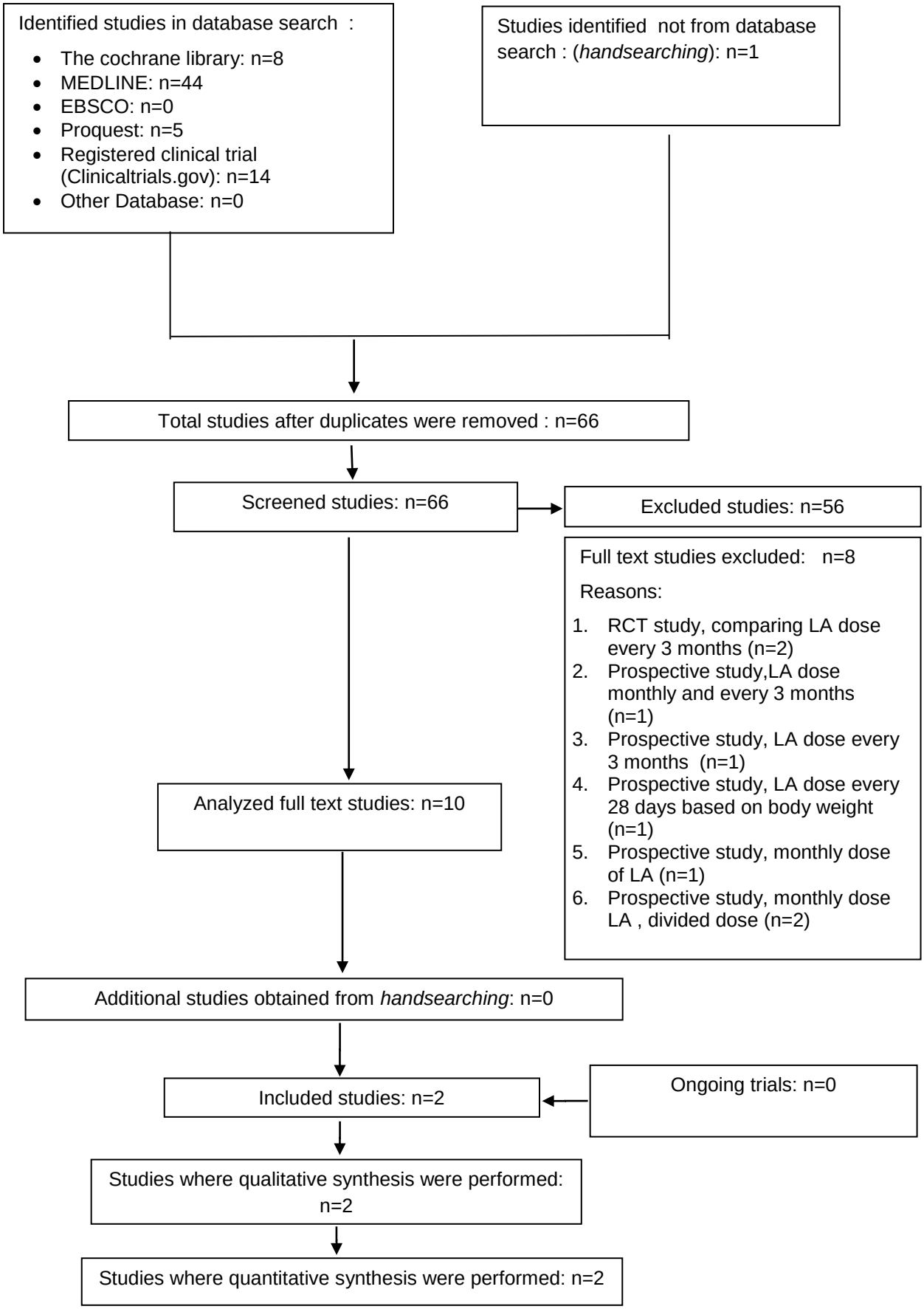
Identified studies in database search :
The cochrane library: n=8
MEDLINE: n=44
EBSCO: n=0
Proquest: n=5
Registered clinical trial (Clinicaltrials.gov): n=14
Other Database: n=0
Studies identified not from database search : (handsearching): n=1
Total studies after duplicates were removed : n=66
Screened studies: n=66
Excluded studies: n=56
Full text studies excluded: n=8
Reasons:
1. RCT study, comparing LA dose every 3 months (n=2)
2. Prospective study,LA dose monthly and every 3 months (n=1)
3. Prospective study, LA dose every 3 months (n=1)
4. Prospective study, LA dose every 28 days based on body weight (n=1)
5. Prospective study, monthly dose of LA (n=1)
6. Prospective study, monthly dose LA , divided dose (n=2)
Analyzed full text studies: n=10
Additional studies obtained from handsearching: n=0
Included studies: n=2
Ongoing trials: n=0
Studies where qualitative synthesis were performed: n=2
Studies where quantitative synthesis were performed: n=2

Figure 1. Workflow of the search result

Two studies were included in the meta-analysis: a study by Fuld (2011) in Philadelphia involving 54 subjects, 49 girls and five boys age 5 to 10 years old; and a study by Mericq (2009) in Santiago, Chile involving 14 subjects, all were girls aged 7 to 9 years old.[14]

Both studies used LA 7.5 mg/month, 11.25 mg/3 months and 22.5 mg/3 months for at least 12 months followed by LH, FSH, growth velocity and bone age examination. One study used intention-to-treat analysis, while the other used per protocol analysis.[15]

Table 1. Overview of the included study population

Study	Intervention (I) and control (C) (mg)	Country	(N) *Randomized*	(N) *Randomized finishing study*	Gender (girl, N)	Age [mean (SD)/range of year]	*Follow-up (year)*
Fuld,	I: LA 11.25	USA	22	21	21	8.1±1,4	2
2011	C: LA 7.5	USA	21	19	19	8.3±2,2	2
	Total		43	40	40		
	I: LA 22.5	USA	16	14	14	7.8±2,2	2
	C: LA 7.5	USA	21	19	19	8.3±2,2	2
	Total		37	33	33		
	I: LA 22.5	USA	16	14	14	7.8±2,2	2
	C: LA 11.25	USA	22	21	21	8.1±1,4	2
	Total		38	35	35		
Mericq,	I: LA 11.25	Chile	4	4	4	8.9±0,4	1
2009	C: LA 7.5	Chile	5	5	5	7.5±0,2	1
	Total		9	9	9		
	I: LA 22.5	Chile	5	5	5	9.2±0,3	1
	C: LA 7.5	Chile	5	5	5	7.5±0,2	1
	Total		10	10	10		
	I: LA 22.5	Chile	5	5	5	9.2±0,3	1
	C: LA 11.25	Chile	4	4	4	8.9±0,4	1
	Total		9	9	9		
Total	All I		47	44			
	All C		52	49			
	All I + C		99	93			

LA: *Leuprolide acetat*e

Primary outcome: **Luteinizing Hormone (LH) suppression**

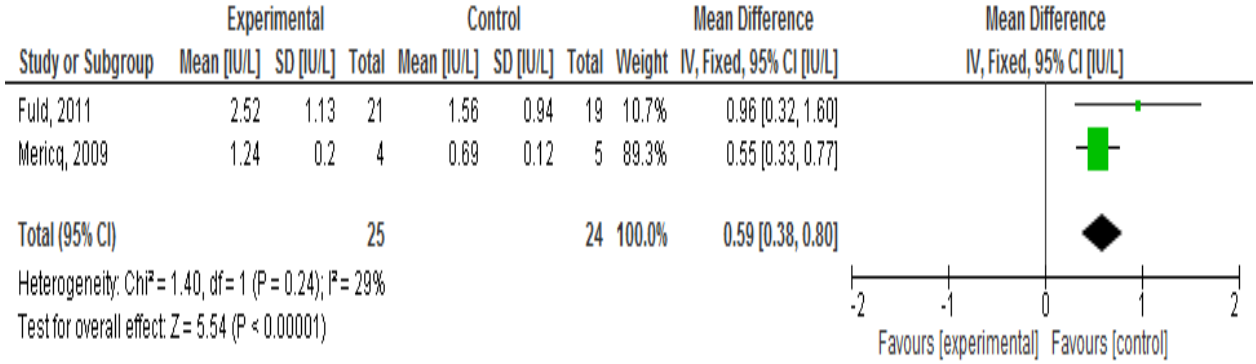

Figure 2. *Forest plot* of the effect of LA dose 11.25 mg/3 months compared to dose 7.5 mg/month (control) for 1 year on LH level

The meta-analysis showed significant differences in the suppression of LH level, 0.59 (CI 95% 0.38; 0.80) IU/L in LA 7.5 mg/month (control) compared to 11.25 mg/3 months. The results, shown in figure 2, were statistically significant, with low heterogeneity (I^2 =29%; p=0.24). Fuld, et al showed a significant LH suppression of 0.96 (CI 95% 0.32; 1.60) IU/L.

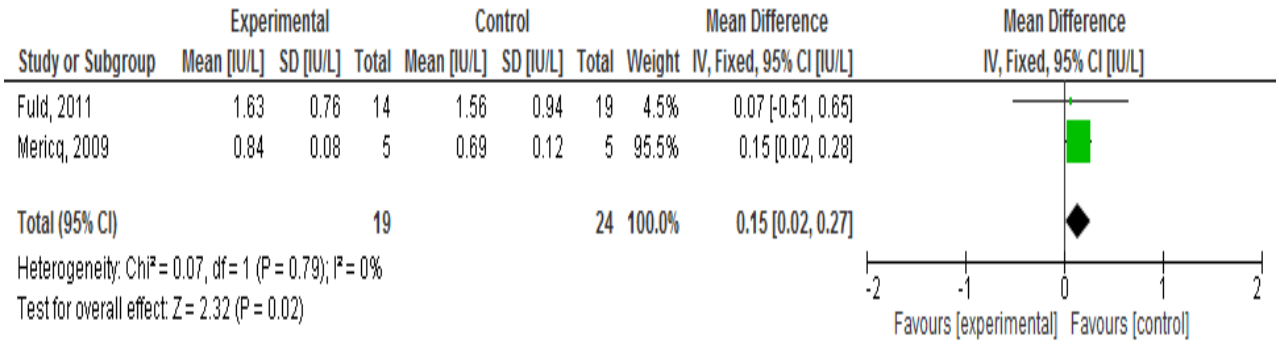

Figure 3. *Forest plot* of the effect of LA dose 22.5 mg/3 months compared to 7.5 mg/month (control) for 1 year on LH levels.

LH supression was significant [0.15 (CI 95% 0.02; 0.27) IU/L] with LA 7.5 mg/month (control) administration compared to 22.5 mg/3 months. The result were statistically significant, with low heterogeneity (I^2 =0%; p=0.79), and can be seen in figure 3. Mericq, et al found significant LH suppression of 0.15 (CI 95% 0.02; 0.28) IU/L.

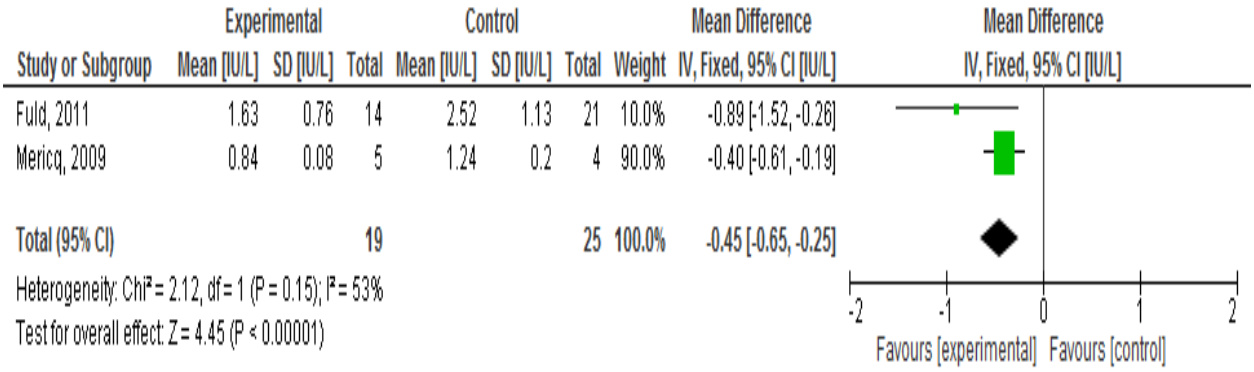

Figure 4. *Forest plot* of the effect of LA dose 22.5 mg/3 months and 11.25 mg/3 months (control) on LH levels.

Figure 4 shows the effect of LA dose 22.5 mg/3 months compared to 11.25 mg/3 months. Significant differences were found in the suppression of LH level of -0.45 (CI 95% 0.65; - 0.25) IU/L with LA 22.5 mg/3 months compared to 11.25 mg/3 months (control), the heterogeneity was low (I^2 =53%; p=0.15). The study by Fuld showed a higher effect in LH suppression, which was - 0.89 (CI 95% - 1.52; 0.26) IU/L.

Secondary outcome: Growth velocity

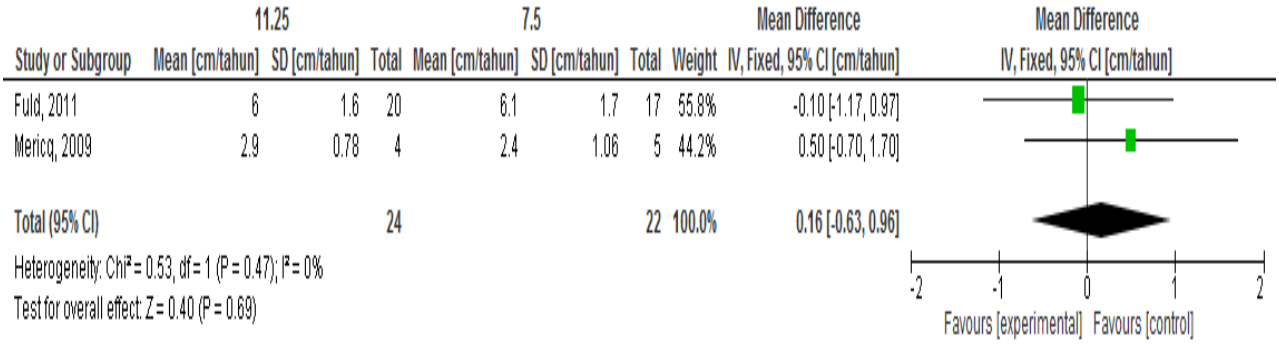

Figure 5. *Forest plot* of the effect of LA dose 11.25 mg/3 months and 7.5 mg/month (control) for 1 year on growth velocity

Growth velocity was not significantly different in the group receiving LA 7.5 mg/month (control) compared to 11.25 mg/3 months, mean difference was 0.16 (CI 95% -0.63; 0.96) cm/year. Heterogeneity was low (I^2 =0%; p=0.47).

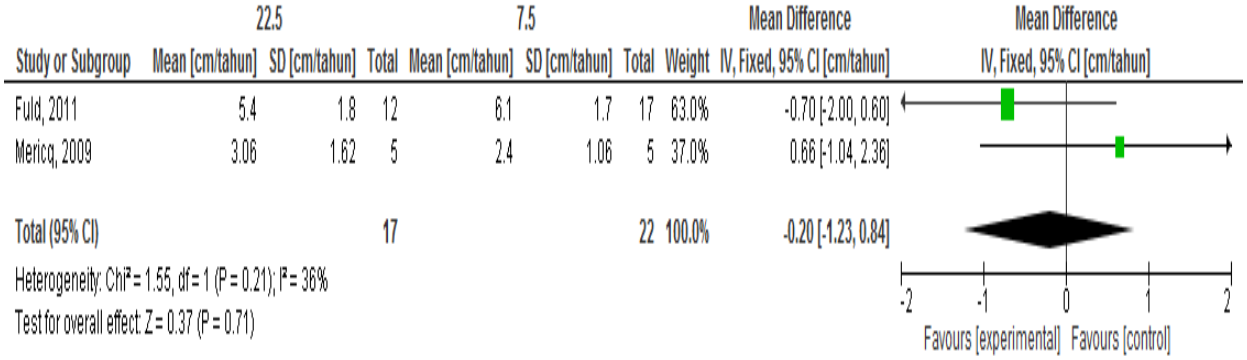

Figure 6. *Forest plot* of the effect of LA 22.5 mg/3 months compared to 7.5 mg/month (control) for 1 year on growth velocity.

No differences in growth velocity were found between LA 7.5 mg/month (control) compared to 22.5 mg/3 months, with the mean difference -0.20 (CI 95% -1.23; 0.84) cm/year and low heterogeneity (I^2 =36%; p=0.21). This result can be seen in figure 6.

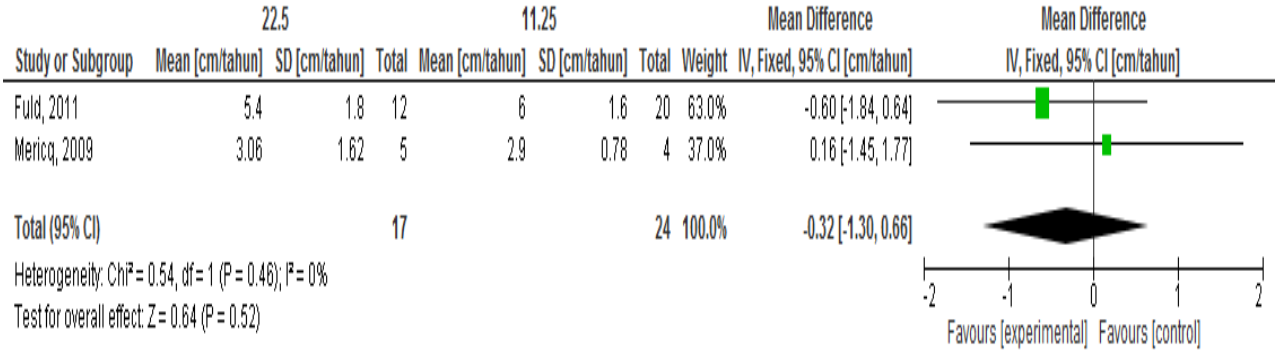

Figure 7. *Forest plot* of the effect of LA 22.5 mg/3 months and 11.25 mg/3 months (control) on growth velocity.

Growth velocity was also not statistically significantly different between LA 22.5 mg/3 months compared to 11.25 mg/3 months (control), mean difference was -0.32 (CI 95% -1.30; 0.66) cm/year. Heterogeneity was low (I^2 =0%; p=0.46). These results are shown in Figure 7.

Discussion

The meta-analysis from two studies which compared the effect of LA 7.5 mg/month, 11.25 mg/3 months, and 22.5 mg/3 months on LH suppression showed statistically significant results. The administration of LA 7.5 mg/month resulted in higher LH suppression compared to 11.25 mg/3 months and 22.5 mg/3 months, each with 0.59 (CI 95% 0.38; 0.80) IU/L and 0.15 (CI 95% 0.02; 0.27) IU/L after one year of follow up. On the other hand, LA dose of 22.5 mg/3 months resulted in LH suppression higher than 11.25 mg/3 months; -0,45 (CI 95% -0,65; -0,25) IU/L.

This result is in accordance with Fuld (2011) and Mericq (2009) who observed that high and monthly dose of LA for CPP might be needed in some conditions, and adequate dosage is important for an optimal outcome. [14,15] Fuld obtained no significant difference in LH suppression between 7.5 mg/month compared to 22.5 mg/3 months. Since LA injections every three months are preferable compared to monthly injections, the former are recommended for routine use, even though monthly injections are approved by *Food and Drug Administration* (FDA) in the USA for CPP treatment.

Theoretically, monthly injections with lower total dose compared to three-months injections may result in better LH suppression and clinical outcome. A study comparing monthly and three-months LA injections showed that continuous monthly injections were not preferable nor recommended. There are two approaches for routine LA injections per three months: every subject were given LA 22.5 mg/3 months, almost equal to the total dose of monthly injections, or starting from 11.25mg/3 months which was effective in most cases and can be increased if hormonal criteria were met or the patient's symptoms were clinically persistent. [15]

In this meta-analysis, LA 7.5 mg compared to 11.25 mg/3 months and 22.5 mg/3 months on growth velocity after one year of follow up was not statistically significantly different. This result is consistent with a study by Fuld (2011) which showed indifference of growth velocity in all groups, and in accordance with regression in normal pre-pubertal subjects during treatment. Fuld, et al followed the subjects for two years, yet no significant difference was found in terms of declining growth velocity during the second year of treatment. Growth velocity in boys and girls were equal (5.4 cm per year in the first year).[15,16]

In Fuld's study (2011), LA treatment every three months showed a decrease in LH stimulation and estradiol concentration around ten times from the baseline and remained for two years. Bone age (BA) and growth velocity (GV) development were both suppressed for two years, either with monthly or every three months preparations. Three subjects in Fuld's study showed LH level >6 IU/L during therapy; one from each group. A girl aged two years with hypothalamus hamartoma in the group receiving 22.5 mg/3 months showed persistent increase in LH level 7-8 IU/L during 36 weeks of follow up. Then, the treatment was replaced with histrelin implant which produced higher suppression rates. A girl received monthly LA injections showed a progressively increased LH level up to 12 IU/L in 24 weeks accompanied by increased injection reaction, which improved after the regiment was changed to daily leuprolide. [15]

In a study by Mericq (2009), GnRH stimulating peak LH <2 IU/L, which was the main effect criteria, was observed in 80% case with treatment dose of 7.5 mg/month, in 75% with 11.25 mg/3 months, and 100% with 22.5 mg/3 months within six months of treatment. After 12 months, 100% patients had their LH level suppressed until <2 IU/L. This result showed that injections given every three months is preferable for children with CPP. Furthermore, LH suppression is achieved faster in dose 22.5 mg/3 months compared to dose 11.25 mg/3 months; therefore adequate dose is important to achieve optimal effects. Further researches with longer duration of follow up for final height is needed, as well as for patients who weigh more than 30 kg Theoretically, LA dose of 22.5 mg/3 months is equal to 7.5 mg/month, while 11.25 mg/3 months is equal to a smaller monthly dose.

On study enrollment, the girls were in *Tanner stage* 2 (n=3), *Tanner stage* 3 (n=3), *Tanner stage* 4 (n=7), and *Tanner stage* 5 (n=1). None of them had menarche when LA treatment started. Breast Tanner stage did not change in seven of 14 girls, four of 14 girls had regression and breast stage progression was observed in three girls. One of the girls also experienced increased ovarium volume. Two girls were included in the group receiving LA 11.25 mg/3 months, which was the lowest dose given per month, and one girl in group receiving 7.5 mg/month. None of the three girls received LA dose of 22.5 mg/3 months.[14,17]

Bone age was delayed in all groups and there was no significant difference between the groups, although the duration of follow up (12 months) was considered short to evaluate bone age maturation rate. This result indicated that the dose given every three months might be too low. This study also showed that the increasing adult height was predictive in all groups, even though the duration of follow up was too short to be certain. [14] Other studies showed that patients with lower LH level have a higher adult final height prediction. Higher estradiol suppression can lead to slower bone maturation, slower pubertal progression and higher increase in final body height. While some studies confirm this theory, further researches are needed to see the long-term outcomes. Rapid changes in bone maturation associated with CPP can decrease adult height due to premature fusion of the epiphyseal growth plates.[18,19,20]

It is important to determine any clinical benefits from higher LH suppression. The cost-benefit ratio is also important to analyze higher and more expensive doses toward growth velocity. Long-term data on final body height is necessary to make such analysis.[14] Due to its high cost, treatment with GnRHa must be carefully considered. Adequate suppression must be obtained to achieve optimal results. Treatment must be given individually. Age on presentation, as well as the rate of pubertal acceleration and growth, should be taken into consideration. Girls whose height potential does not decrease might not need GnRHa treatment. If the pubertal growth spurt has already occurred and the BA is already mature, treatment might not be of much use, unless given for psychosocial reasons, such as to prevent early menstruation .[9,21-23]

This study concluded that LA injections every three months are a satisfying choice for treatment in children with CPP to avoid monthly injections. LH suppression occurred faster when given LA with the dose 22.5 mg/3 months compared to dose 11.25 mg/3 months; therefore, adequate dose important to achieve optimal outcomes. Further studies are needed in patients with body weight more than 30 kg and with longer therapy duration with final body height analysis.[14,24]

Fuld's study had a relatively larger sample size (n=54), but the value was small, while Mericq's study provided greater value although only involving a small sample (n=14). These results occured because studies with small standard deviation (SD) have a relatively greater value, while studies with big SD have a relatively small value. This is appropriate if SD variation among studies reflect differences in results measurement realibilities, but it might not be appropriate if difference in SD reflect significant difference within results variability in the study population.[25]

The weakness of this meta-analysis is the limited total sample size in the RCTs and follow up was done for only one year. Moreover, the two RCTs included in this study were not free of bias because concealment and blinding were not conducted.

Conclusion

LA 7.5 mg/month dose provided greater LH suppression compared to 11.25 mg/3 months dose, while LA therapy with the dose of 22.5 mg/3 months showed higher suppression compared to 11.25 mg 3-months formulation. There were no differences in growth velocity from LA dose variety and time of administration. High dose of LA given every three months can be considered to ensure compliance in patients with conditions not appropriate to be given LA every month. Clinical trials are needed to compare variability of monthly and three-months doses to evaluate the most optimal effects on LH, FSH, and estradiol levels suppression, growth velocity, and bone age with administration of different doses.

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