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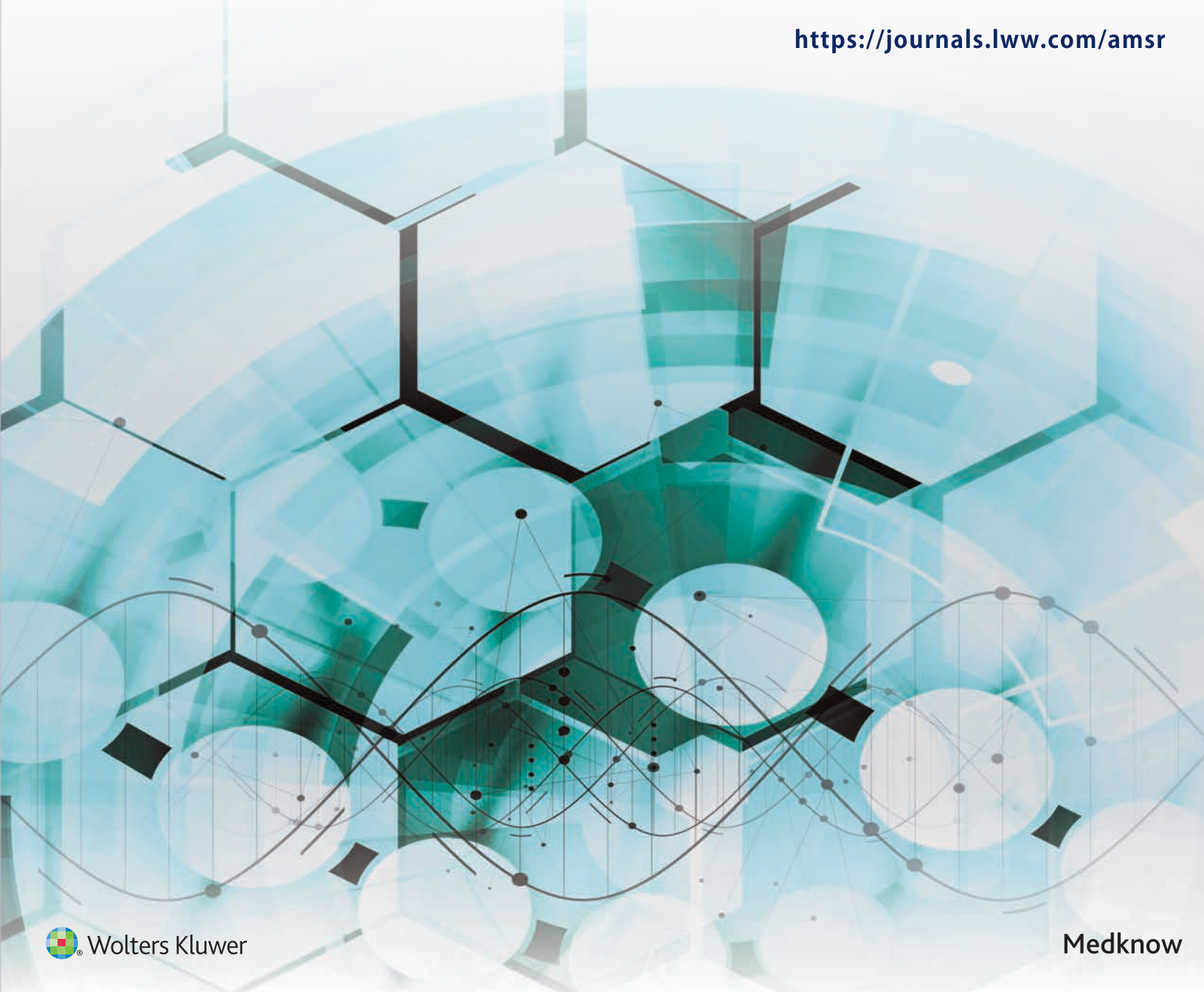

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Review Article

Effects of clomiphene citrate and anastrozole as a combination therapy for hypogonadism: A systematic review and meta-analysis

Padmashobana Bagavathithasan, Swati Sucharita Dash, Lakshmi Venkatachalam, Vaishali Amol Shetye, Shashwati Pankaj, Jignesh Bhate, Guruprasad K. S. Rao

Real-World Evidence & Health Economics and Outcomes Research, Molecular Connections Analytics Pvt. Ltd., Bengaluru, Karnataka, India

Abstract

Clomiphene citrate (CC) and anastrozole (AZ) combination has been used off-label to improve spermatogenesis in male infertility. This systematic literature review and meta-analysis evaluated the efficacy and safety of CC and AZ combination therapy in subfertile hypogonadal men. Studies were systematically searched and retrieved from PubMed, Web of Science, CENTRAL, and ClinicalTrials.gov from inception to May 19, 2021, using MeSH terms/keywords. Statistical analysis was performed using a random effects model, pooled risk ratio, and heterogeneity (I^2). The methodological quality of the studies was assessed utilizing the Newcastle–Ottawa Scale and Moga tools. Overall, 37 studies were identified from a systematic search, and two studies that met the eligibility criteria were considered for quantitative synthesis. Treatment with combination therapy (CC + AZ) and monotherapy (CC) significantly increased the total testosterone (TT), bioavailable testosterone (BT), estradiol level, and testosterone/estradiol (T/E) ratio from baseline ($P < 0.00001$). In comparison with monotherapy, combination therapy increased TT (mean difference [MD]: 56.29; 95% confidence interval [CI], 12.36, 100.22; $P = 0.01$) and BT (MD: 48.18; 95% CI, 8.19, 88.17; $P = 0.02$) levels in blood. Monotherapy elevated the estradiol level and decreased T/E ratio, whereas combination therapy reduced the estradiol (MD: -2.17; 95% CI, -59.89, 55.55; $P = 0.94$) level and optimized T/E ratio (MD: 3.64; 95% CI, -18.90, 26.18; $P = 0.75$). P-specific antigen and hematocrit levels were measured to evaluate the safety of combination and monotherapy. Combination therapy with CC and AZ was safe and well-tolerated in hypogonadal men.

Keywords: Anastrozole, clomiphene citrate, hypogonadism, estradiol, testosterone

Key Messages:

- Clomiphene citrate (CC) and anastrozole (AZ) are considered affordable alternatives to exogenous testosterone for the treatment of hypogonadism.
- The combination therapy is proven to be an effective and safe therapy for infertile male patients.

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INTRODUCTION

Clomiphene citrate (CC) and anastrozole (AZ) are considered inexpensive alternatives to exogenous testosterone and other injectables for the treatment of hypogonadism, a condition characterized by testosterone deficiency and consequent erectile dysfunction in men.[1,2] CC is a selective estrogen receptor modulator that elevates gonadotropin and testosterone levels, while AZ inhibits aromatase and reduces testosterone to estradiol conversion, thereby increasing testosterone levels.[3] Findings from clinical studies show that CC + AZ combination results in improved outcomes than CC monotherapy in infertility treatment.[4–7] This systematic review and meta-analysis aimed to assess the efficacy and safety of CC + AZ combination therapy versus CC monotherapy in the treatment of male hypogonadism.

MATERIALS AND METHODS

Literature search

This systematic review has been conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table S1). PubMed/MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases were electronically searched for publications prior to May 19, 2021, using MeSH terms/keywords related to male infertility, hypogonadism, CC, AZ, and their aliases. Literature search details from the PubMed database are summarized in Supplementary Table S2. Studies were also hand-searched from the reference lists of relevant articles.

Study selection

Studies were selected based on compliance with predefined inclusion and exclusion criteria. Inclusion criteria: (i) adult male patients (≥18 years) with hypogonadism (defined as total testosterone [TT] level of <300 ng/dL or bioavailable testosterone [BT] of <155 ng/dL and accompanied by hypogonadal symptoms or a complaint of infertility); (ii) treatment comparison between CC monotherapy and CC + AZ combination therapy; (iii) report at least one of the following outcomes: TT levels, BT levels, estradiol levels, testosterone/estradiol (T/E) ratio; (iv) Randomized controlled trial (RCT) or observational studies; (v) articles in English language. Exclusion criteria: Study designs other than RCTs and observational studies (case reports/series, systematic reviews, meta-analyses, cross-sectional studies, cross-over studies, and review articles), such as letters to editors, comments, or conference abstracts.

Data extraction and quality (risk of bias) assessment

Two independent researchers were involved in all stages of study selection and data collection. Preliminary screening was carried out based on the title and abstract, followed by the screening of full texts. The included studies were systematically reviewed, and data extraction was performed, if the parameter of interest was reported. Data pertaining to baseline characteristics, participants, interventions, and trial outcomes were extracted independently by the researchers. The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of the included studies. NOS is widely used for observational (both cross-sectional and longitudinal) studies to evaluate study quality and risk of bias. It evaluates three quality parameters such as selection, comparability, and outcome, which are further categorized into eight specific items. A star system was developed for assessing the aforementioned parameters. A maximum of one star for the selection and outcome categories; maximum of two stars for the comparability category denotes the quality of the included study.[8,9] Risk of bias for case series was assessed using Moga tools.[10] Disagreements between the reviewers were resolved by consensus following discussion.

Endpoints of meta-analysis

The efficacy of interventions was evaluated based on changes in the levels of TT, BT, estradiol, and T/E ratio. P-specific antigen (PSA) and hematocrit levels were measured after 6 months to evaluate the safety of combination and monotherapy with CC + AZ and CC, respectively, in hypogonadal men.

Data analysis

I^2 statistic was used to test statistical heterogeneity, where values >50% represent important heterogeneity.[11,12] Outcomes were pooled using mean differences (inverse variance [IV] method) and Mantel–Haenszel risk ratio (RR) with 95% confidence intervals (CI). A random-effects model was used in all outcomes as the selected studies differed in terms of participants, interventions, study duration, along with other clinical heterogeneity.[13] Meta-analysis was performed using Review Manager (RevMan) (Computer program) Version 5.4, The Cochrane Collaboration, 2020. Numerical values from the graphs, if any, were extracted using Web Plot Digitizer.[14] In all the analyses, a P-value < 0.05 (two-tailed test) was considered to be statistically significant.

RESULTS

Study selection and characteristics of included studies

PRISMA flowchart depicts the selection of included studies [Figure 1]. A total of 37 published studies were identified from

database searches and screened for eligibility. Of these, 35 studies were excluded at title and abstract level based on the population (n = 3), intervention (n = 8), comparator (n = 1), outcomes (n = 3), publication type (n = 7), study design (n = 2), and duplicates (n = 11). Two studies comprising 369 hypogonadism patients (n = 51[15] and n = 318[16]) that met the eligibility criteria were included for the data extraction and meta-analysis. Detailed characteristics of included studies are given in Table 1.

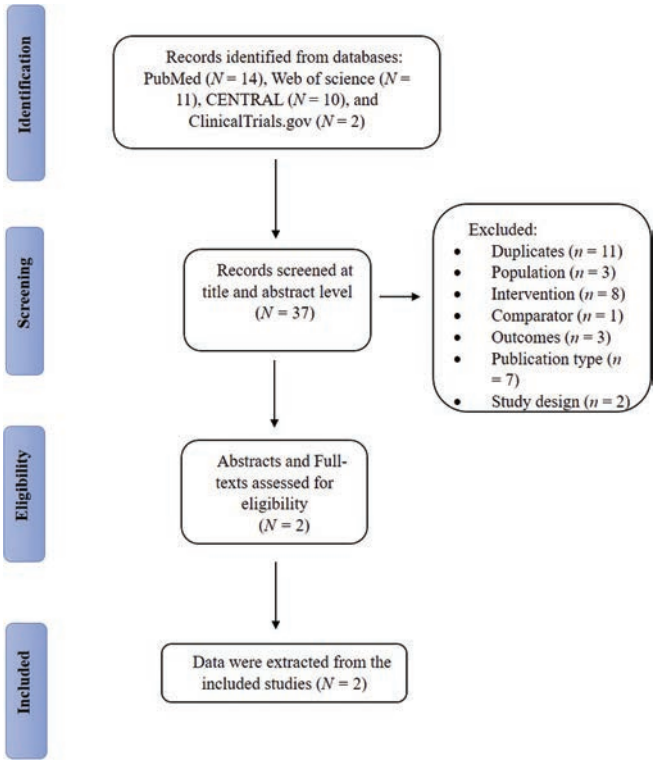

Figure 1: PRISMA flowchart for selection and inclusion of studies. *N*, total number of records; CENTRAL, Cochrane Central Register of Controlled Trials

The included retrospective studies were conducted in 2018[15] and 2020[16] that compared the efficacy and safety of CC monotherapy with CC + AZ combination therapy. The treatment was initiated with CC monotherapy (N = 369), followed by CC + AZ combination therapy in a proportion of subfertile hypogonadal male patients (N = 148), and the remaining continued with CC monotherapy (N = 221). In the study by Alder *et al.*[15], AZ was administered to the subfertile hypogonadal men after 2.3 months of CC monotherapy and in a study by Keihani *et al.*[16], obese patients with baseline estradiol levels of ≥18.5 pg/mL were subjected to combination therapy. The duration of CC monotherapy in the two studies was 1 month and 2.3 months, respectively. The median follow-up duration was 8.4 months[15] and 9 months[16] respectively. Both the included studies evaluated levels of TT, BT, estradiol, and T/E ratio as key outcomes.

Comparison of CC + AZ combination and CC monotherapy on hormone profiles against baseline

TT level

Both the included studies evaluated the effect of CC + AZ combination therapy and CC monotherapy on TT levels with respect to baseline. Overall results suggested

Table 1: Characteristics of included studies

S. no.	Study ID; year; country	Study design	Sample size; mean age (years); patient characteristics	Intervention/dose/duration	Comparator	Patient baseline characteristics	Outcomes measured
1	Alder *et al*., 2018; USA	Retrospective	51; 35.4; Hypoandrogenic subfertile men	CC + AZ (combination therapy) CC–25–100 mg daily AZ–1 mg twice to thrice weekly (dosage was titrated based on the patient's response) Follow-up for <6 months and ≥6 months	CC (Monotherapy) CC–25–100 mg daily (dosage was titrated based on the patient's response) Follow-up for 3.2 months	Total testosterone 257.6 ng/dL; Bioavailable Testosterone 147.3 ng/dL; Estradiol 21 pg/mL; LH 4.7 mIU/L; FSH 5.1 mIU/L; SHBG 25.6 nmol/L	Total testosterone, bioavailable testosterone, estradiol, testosterone/estradiol ratio
2	Keihani *et al*., 2020; USA	Retrospective	318; 34; Hypogonadal men	CC + AZ (combination therapy) CC–25–100 mg daily AZ–1 mg twice weekly dosage was titrated based on the patient's response) follow-up for 3-6 months	CC (monotherapy) CC–25–100 mg daily (dosage was titrated based on the patient's response) follow-up for 3–6 months	Total testosterone 247 ng/dL; Bioavailable Testosterone 160 ng/dL; estradiol 16.9 pg/mL; LH 4.5 IU/L; FSH 4.4 IU/L; SHBG 24 nmol/L	Total testosterone, bioavailable testosterone, estradiol, testosterone/estradiol ratio

AZ, anastrozole; CC, clomiphene citrate; dL, decilitre; FSH, follicle-stimulating hormone; IU/L, International unit/Litre; LH, luteinizing hormone; mg, milligram; ng, nanogram; nmol/L, nanomoles/litre; mIU/L, milli international units/litre; pg/mL, picogram/millilitre; SHBG, sex hormone binding globulin; USA, United States of America

that CC as monotherapy (mean difference [MD]: 365.50; 95% CI: 292.57, 438.44; $P < 0.00001$; $I^2 = 72\%$) or in combination with AZ (MD: 429.85; 95% CI: 396.57, 463.12; $P < 0.00001$; $I^2 = 0\%$) significantly increased TT levels from baseline (pretreatment) in hypogonadal men within 6 months of treatment [Figure 2A and B]. A significant increase in TT level was also observed post 6 months of treatment with the combination therapy (MD: 372.60; 95% CI: 278.69, 466.51; $P < 0.00001$)[15,16] [Figure 2A]. Heterogeneity was not observed between the studies for postcombination therapy; however, heterogeneity was high in the postmonotherapy group.

BT level

Treatment with CC + AZ combination therapy (MD: 241.41; 95% CI: 203.97, 278.86; $P < 0.00001$; $I^2 = 0\%$) and monotherapy (MD: 199.60; 95% CI: 134.56, 264.64; $P < 0.00001$; $I^2 = 74\%$) significantly increased the BT levels from baseline within 6 months [Figure 3A and B], which is similar to the results reported in the individual studies [Figure 3A and B]. An increase in BT levels was also observed post 6 months of treatment with the CC + AZ combination therapy (MD: 207.60; 95% CI: 35.82, 379.38; $P = 0.02$) as seen in one included study[15] [Figure 3A].

Estradiol level

A significant increase in estradiol levels was observed in hypogonadal men treated with combination therapy (MD: 26.81; 95% CI: -0.34, 53.95; $P = 0.05$; $I^2 = 98\%$) as well as CC monotherapy (MD: 31.13; 95% CI: 5.07, 57.20; $P = 0.02$; $I^2 = 98\%$) within 6 months and with combination therapy (MD: 12.60; 95% CI: 4.85, 20.35; $P = 0.001$) after 6 months [Figure 4A and B]. Heterogeneity was high between the two included studies. Meta-analysis results correlated with the findings reported in the individual-included studies.

T/E ratio

Treatment with CC + AZ combination therapy post-treatment (≤6 months) increased T/E ratio [Figure 5A], although the increase was not statistically significant (MD: 5.44; 95% CI: -8.17, 19.05; $P = 0.43$; $I^2 = 95\%$). High heterogeneity was observed between the studies. However, a significant increase in T/E ratio was also observed with the combination therapy after 6 months (MD: 10.60; 95% CI: 5.43, 15.77; $P < 0.0001$) of treatment in one of the included studies.[15] Within 6 months of treatment with CC monotherapy, no significant difference was observed between baseline and T/E ratio (MD: -0.10; 95% CI: -4.90,

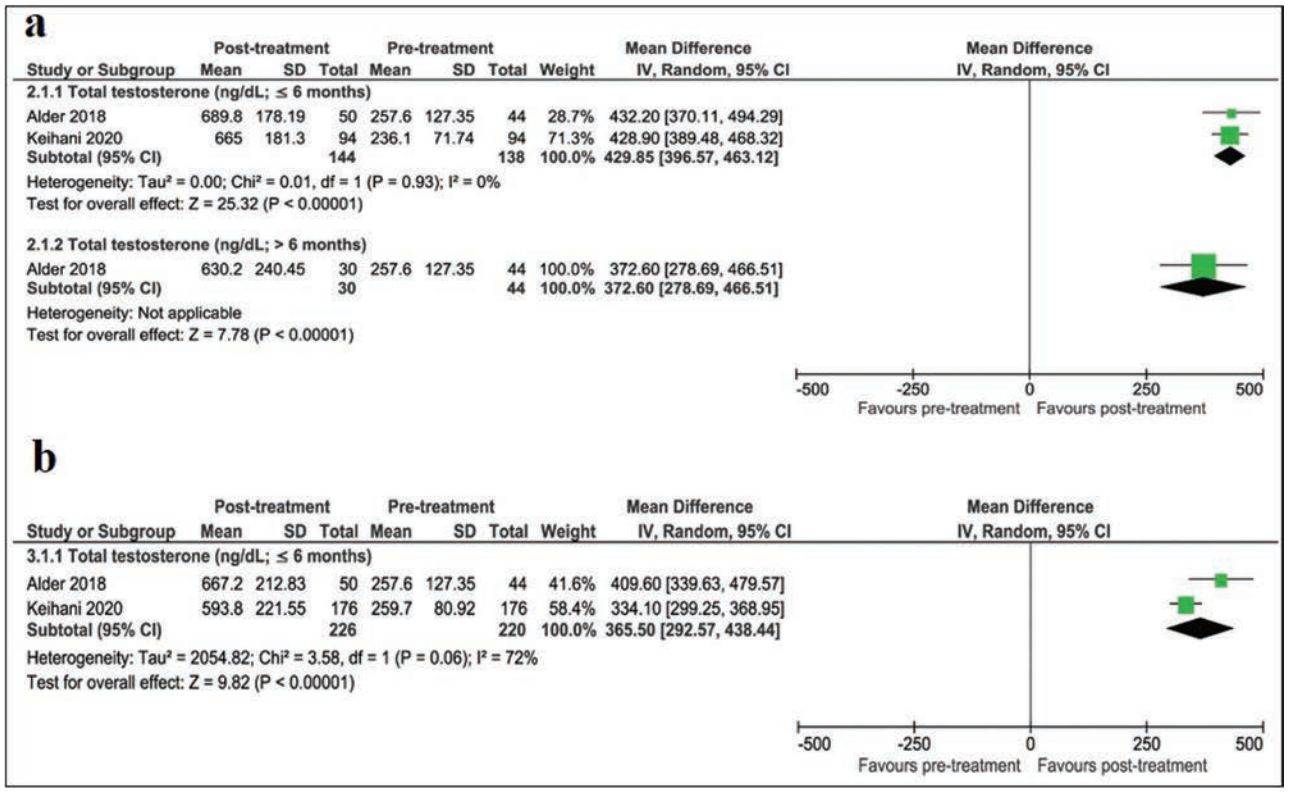

Figure 2: Mean differences in total testosterone levels (ng/dL) during post- and pretreatments with (A) combination (CC + AZ) and (B) monotherapy (CC) in patients with hypogonadism. CI, confidence interval; df, degrees of freedom; SD, standard deviation; I^2, measures the percentage variability in the treatment effect estimates that is due to between-study heterogeneity rather than chance; Tau, estimated standard deviation in random-effects model, underlying true effects (Tau^2 is the variance); *P*-value <0.05 statistical significant; *Z*, the significant test for the weighted average effect size, conducted on a population that follows a normal distribution; Chi^2, a statistical test for determining the difference between treatments

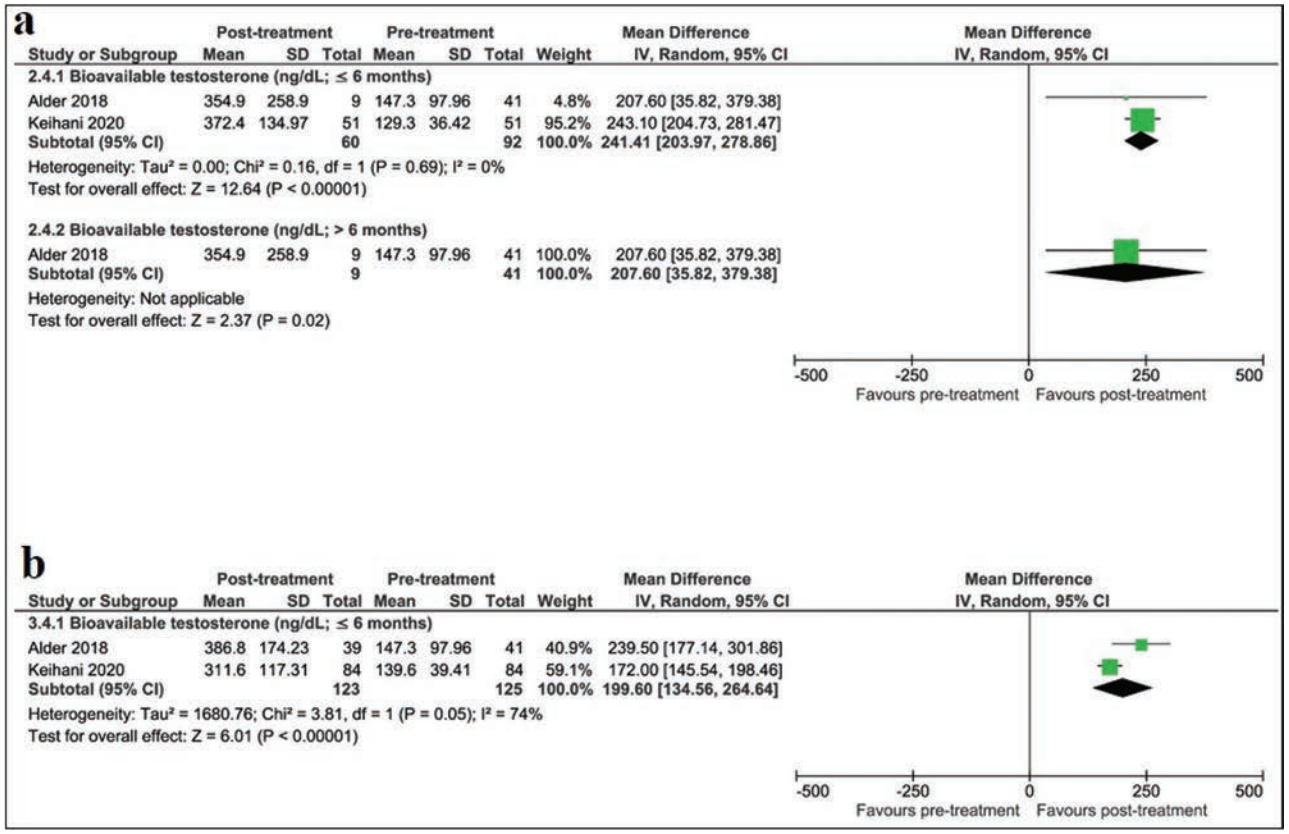

Figure 3: Mean differences in bioavailable testosterone levels (ng/dL) during post- and pretreatments with (A) combination (CC + AZ) and (B) monotherapy (CC) in patients with hypogonadism. CI, confidence interval; df, degrees of freedom; SD, standard deviation; I^2, measures the percentage variability in the treatment effect estimates that is due to between-study heterogeneity rather than chance; Tau, estimated standard deviation in random-effects model, underlying true effects (Tau^2 is the variance); *P*-value <0.05 statistical significant; *Z*, the significant test for the weighted average effect size, conducted on a population that follows a normal distribution; Chi^2, a statistical test for determining the difference between treatments

4.70; $P = 0.97$; $I^2 = 91\%$). There was a high heterogeneity observed between the studies [Figure 5A and B].

Comparison of the effect of CC + AZ combination therapy with CC monotherapy on hormone profile

Both the included studies reported the effect of CC monotherapy and CC + AZ combination therapy on TT levels in hypogonadal men. In the present meta-analysis, 144 patients on combination therapy and 226 patients on CC monotherapy were included. An increase in TT level significantly favored CC+AZ combination therapy compared to CC monotherapy (MD: 56.29; 95% CI: 12.36, 100.22; $P = 0.01$; $I^2 = 8\%$), which also correlated with the findings reported in the individual studies. There was no heterogeneity observed between the studies [Figure 6A].

Increased BT levels significantly favored combination therapy than monotherapy (MD: 48.18; 95% CI: 8.19, 88.17; $P = 0.02$; $I^2 = 5\%$). Similar results were obtained in the individual studies. The heterogeneity observed between the studies was low [Figure 6B].

Statistically significant differences were not observed in estradiol levels between the combination therapy and monotherapy (MD: -2.17; 95% CI: -59.89, 55.55; $P = 0.94$; $I^2 = 99\%$). The heterogeneity was high between both studies [Figure 6C]. Similarly, there was no significant difference between CC + AZ combination therapy and CC monotherapy with respect to T/E ratio, as observed in the present meta-analysis [Figure 6D]. Heterogeneity between the studies was significantly high (MD: 3.64; 95% CI: -18.90, 26.18; $P = 0.75$; $I^2 = 98\%$) [Figure 6D].

Risk of bias

Risk of bias analysis has been summarized in the Supplementary Tables S3 and S4. Included studies[15,16] did not show any competing interest. The risk of bias was not observed in this systematic literature review (SLR), and the included studies had good and acceptable quality.

Safety

Combination therapy (CC + AZ) did not show any adverse effects in hypogonadism patients (Alder *et al.*, [*n* = 51];

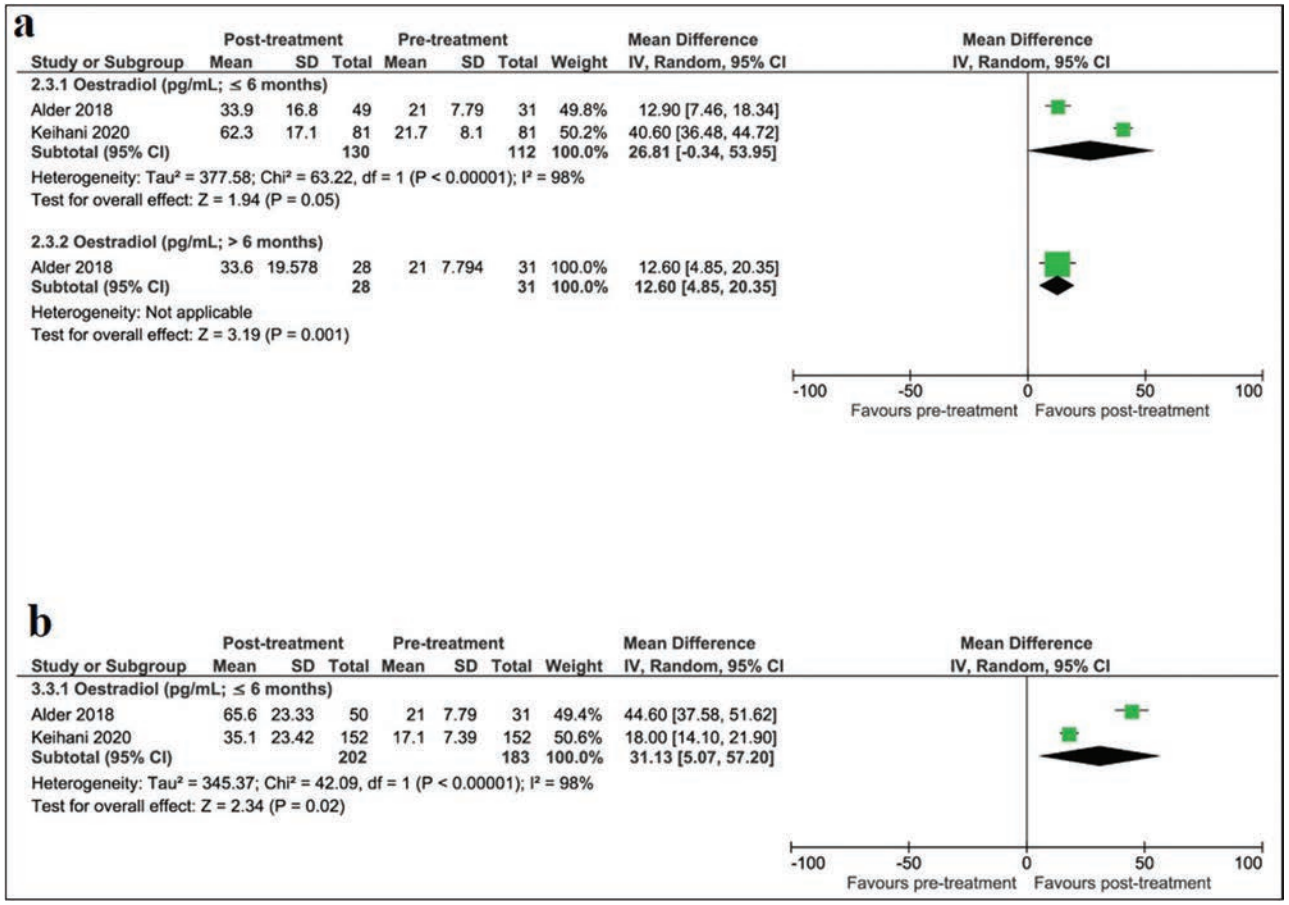

Figure 4: Mean differences in estradiol levels (pg/mL) during post- and pretreatments with (A) combination (CC + AZ) and (B) monotherapy (CC) in patients with hypogonadism. CI, confidence interval; df, degrees of freedom; SD, standard deviation; I^2, measures the percentage variability in the treatment effect estimates that is due to between-study heterogeneity rather than chance; Tau, estimated standard deviation in random-effects model, underlying true effects (Tau^2 is the variance); *P*-value <0.05 statistical significant; Z, the significant test for the weighted average effect size, conducted on a population that follows a normal distribution; Chi^2, a statistical test for determining the difference between treatments

Keihani *et al.*, [*n* = 318]). PSA (1.36 ng/mL) and hematocrit (48.1%) levels remained within the normal range after 6 months of treatment.

DISCUSSION

The present meta-analysis was carried out to demonstrate the effectiveness of combination therapy with CC + AZ in comparison to monotherapy with CC in subfertile hypogonadal men. CC and AZ are the widely used off-label treatment regimens for the management of idiopathic male infertility.[17] To the best of our knowledge, this is the first SLR and meta-analysis to compare CC + AZ combination therapy with CC monotherapy among males with hypogonadism. Levels of TT, BT, estradiol, and T/E ratio were analyzed as the study outcomes.

Post-treatment with combination therapy (CC + AZ), there was a significant elevation in levels of hormones such as TT, BT, and estradiol along with T/E ratio in subfertile hypogonadal men. Similarly, monotherapy with CC also significantly increased TT, BT, and estradiol levels in blood. Previous studies have shown that an increase in testosterone levels with CC treatment proved it to be an effective monotherapy for hypoandrogenism.[18,19] In this study, the post-CC therapy T/E ratio was numerically reduced (MD: -0.10; 95% CI: -4.90, 4.70) in hypogonadism patients. Generally, CC stimulates androgen synthesis by GnRH production in the hypothalamus and is also associated with increased estradiol levels and decreased T/E ratio.[20] Decreased T/E ratio is a characteristic feature of endocrinopathy in men with severe male infertility.[21] Aromatase enzyme potentially converts increasing testosterone into estradiol in Sertoli and Leydig cells.[22] As a result, the increased estradiol suppresses gonadotropin secretion by a negative feedback mechanism in the hypothalamus-pituitary axis, which further decreases testosterone synthesis and sperm production.[23]

AZ, an aromatase inhibitor, reduces the conversion of testosterone into estradiol.[24] CC potentially blocks the negative feedback of estradiol in the hypothalamus and pituitary, whereas AZ reduces the production of estradiol

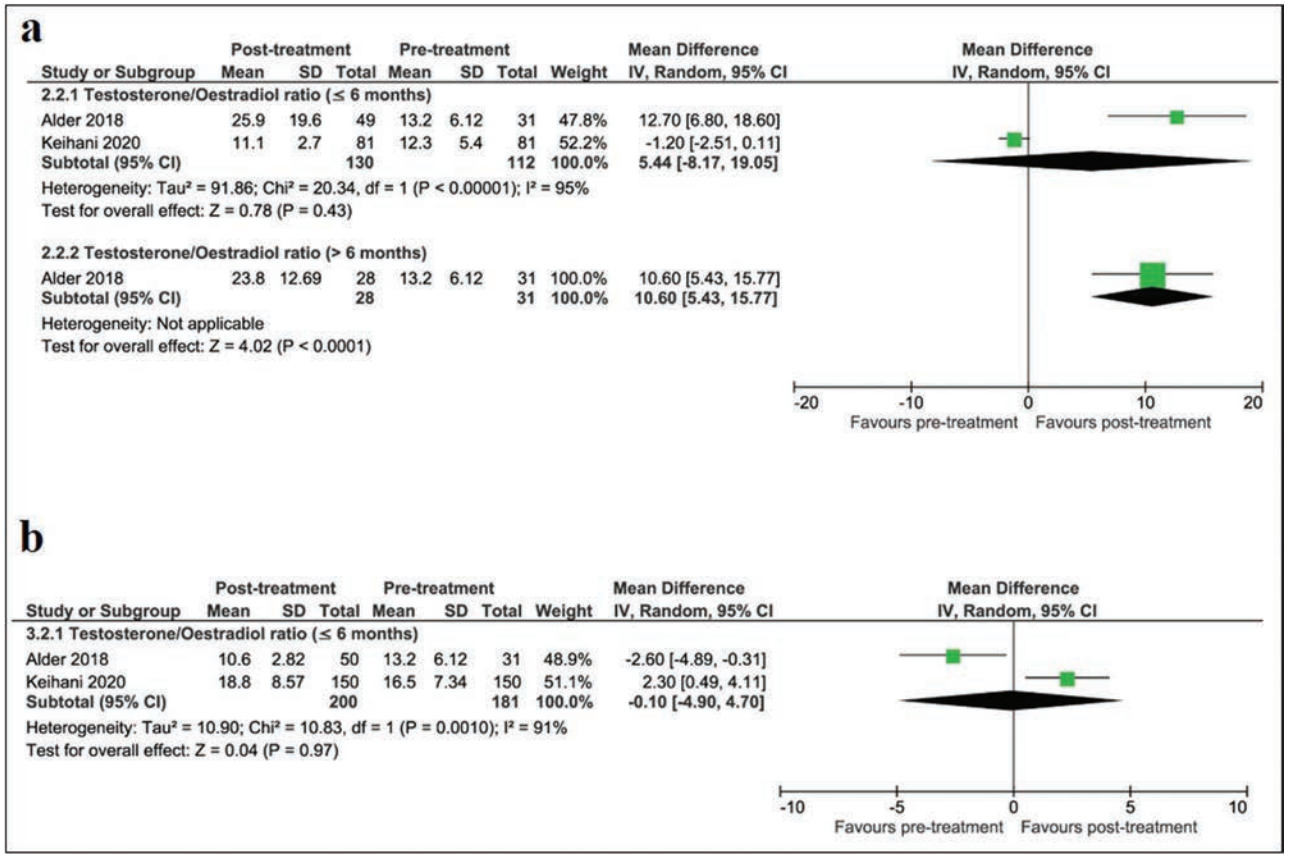

Figure 5: Mean differences in testosterone/estradiol ratio (≤6 months) during post- and pretreatments with (A) combination (CC+AZ) and (B) monotherapy (CC) in patients with hypogonadism. CI, confidence interval; df, degrees of freedom; SD, standard deviation; I^2, measures the percentage variability in the treatment effect estimates that is due to between-study heterogeneity rather than chance; Tau, estimated standard deviation in random-effects model, underlying true effects (Tau^2 is the variance); *P*-value <0.05 statistical significant; *Z*, the significant test for the weighted average effect size, conducted on a population that follows a normal distribution; Chi^2, a statistical test for determining the difference between treatments

by limiting the testicular and peripheral conversion of testosterone. As per this mechanism, CC and AZ have a different effect on the T/E ratio while inducing gonadotropin secretion. This was supported by a randomized prospective, double-blind trial, where CC significantly increased the testosterone level, and AZ showed a significantly higher T/E ratio than CC.[24] Hence, the addition of AZ with CC as a combination therapy optimized the T/E ratio in hypogonadal men.[21] The present meta-analysis results support and correlate with the findings of the clinical trial. In this study, monotherapy significantly increased estradiol levels ($P < 0.00001$) and reduced the T/E ratio from baseline, which is equilibrated by the addition of AZ with CC. Therefore, combination therapy (CC + AZ) can be considered an effective treatment for infertile males. In the study by Kehani *et al.*,[16] among the total number of patients ($n = 318$), 97 hypogonadal men were shifted to combination therapy for improving their T/E ratio to induce spermatogenesis. However, the efficacy and safety of combination therapy versus monotherapy remain unclear, and there is a lack of published evidence on the effects of combination therapy in hypogonadism patients.

In both studies included in this analysis, TT and BT levels increased numerically among patients treated with combination therapy compared to monotherapy. Studies have shown that by competitive inhibition, the estrogen receptor modulator CC successfully boosted endogenous testosterone production,[18] while an aromatase inhibitor increased androgen synthesis and balanced serum testosterone levels in hypogonadal men.[25]

In the present study, monotherapy with CC showed a significant ($P < 0.00001$) rise in the estradiol level from baseline at 3.2 months and 3–6 months as compared to combination therapy, which showed minimal increase within 3 months and no further increase in ≤6 months. Several other studies have also shown that CC in monotherapy increases estradiol levels. An increase in estradiol levels is unwanted in men, which leads to hyperestrogenemic events. In this regard, combination therapy with CC + AZ should be recommended since AZ inhibits aromatase that suppresses testosterone, increasing the incidence of erectile dysfunction.[23] Aromatase inhibitor, AZ, reduces the peripheral and testicular conversion of testosterone

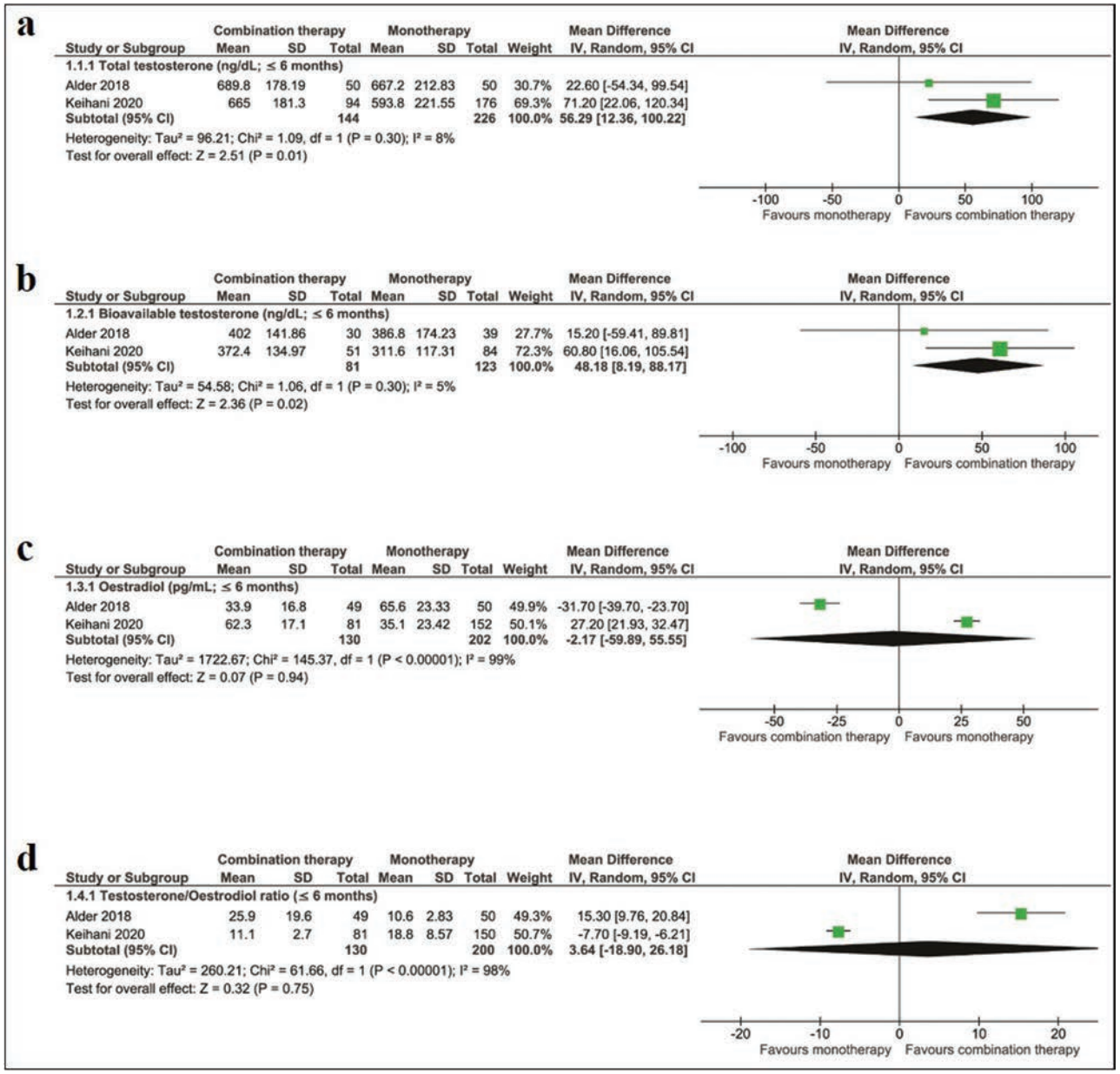

Figure 6: Comparative statistical analysis with the combination (CC + AZ) and monotherapy (CC) on (A) TT, (B) BT, (C) estradiol level, and (D) T/E ratio in hypogonadal men. CI, confidence interval; df, degrees of freedom; SD, standard deviation; I^2, measures the percentage variability in the treatment effect estimates that is due to between-study heterogeneity rather than chance; Tau, estimated standard deviation in random-effects model, underlying true effects (Tau^2 is the variance); *P*-value <0.05 statistical significant; *Z*, the significant test for the weighted average effect size, conducted on a population that follows a normal distribution; Chi^2, a statistical test for determining the difference between treatments

into estradiol, which is beneficial along with CC. In this systematic review, it was observed that the study by Alder *et al.* showed that the addition of aromatase inhibitor with CC reduced the estradiol level when compared to monotherapy; no reduction was observed in the study by Keihani *et al.*[16] Existing literature suggests that 17% of hypogonadal men require the addition of AZ with CC due to the elevated estradiol level with CC monotherapy.[26] Similarly, in the study by Keihani *et al.*,[16] approximately 30% of hypogonadal men needed aromatase inhibitors for reducing their estradiol level, which further led to improved spermatogenesis.

Adverse effects were not seen with combination therapy in hypogonadism patients. In the study by Alder *et al.*,[15] PSA levels were within the normal limits with no reports of prostate cancer after treatment. The present safety results correlate with the findings of Krzastek *et al.*,[27] where CC did not show any significant adverse event in hypogonadism patients. Similarly, a combination of AZ and CC did not exhibit adverse events when used for the improvement of hypogonadal symptoms and erectile function.[28] Hence, combination therapy with CC + AZ is safe and well-tolerated in subfertile hypogonadal men.

STRENGTHS AND LIMITATIONS

This is, to our knowledge, the first time systematic review and meta-analysis have been used in the analysis of available data to comparatively evaluate the safety and efficacy of CC monotherapy and CC + AZ combination therapy in the treatment of hypogonadism in infertile men. In this study, all important outcomes pertaining to male infertility were recorded and analyzed. The current study has some potential limitations that may affect the validity and generalizability of the results. The inclusion of retrospective studies may lead to confounding generalizability and robustness of the findings due to the variation in methodological quality, study design, and the potential of detection bias. The small number and high heterogeneity of the included studies may reduce the reliability and precision of the meta-analysis. Studies in non-English language have been excluded, and the outcomes of these studies, along with unpublished records, could have been negative, different, or null leading to possible biased estimation of treatment outcomes. Another limitation is the lack of lifestyle interventions as a comparator, which may limit the applicability and relevance of the findings. Also, certain outcomes, such as changes in hormone levels, may lack clinical significance without a better comprehension of their implications on patients' general health and quality of life. Thus, further analysis with a larger sample size and well-designed studies are warranted to validate the findings of this study.

CONCLUSION

Combination therapy (CC + AZ) is an effective treatment option for hypogonadal men, which induces androgen synthesis and improves spermatogenesis than monotherapy (CC). The addition of AZ with CC significantly increases TT and BT levels, decreases estradiol levels, and optimizes the T/E ratio in hypogonadism patients. Thus, combination therapy has proved to be an effective and safe therapy for infertile male patients. Considering the lack of previously published systematic reviews and meta-analysis on the combination therapy of CC and AZ, this study may aid the impact on therapeutic decisions in clinical settings while paving the way for exhaustive studies in the future.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Supplementary Table S1: PRISMA checklist for Systematic Review and Meta-analysis

Section/topic		Checklist item	Yes/no
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes
Abstract			
Structured summary	2	Provide a structured summary (IMRAD) including, as applicable: **Introduction** (objectives); **Methods** (study eligibility criteria, participants, and interventions; study appraisal and synthesis methods); **results**; **Discussion (**limitations, conclusions, and implications of key findings) **systematic review registration number (PROSPERO)**	No
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Yes
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	
Methods			
Protocol and registration	5a	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information, including registration number	Yes
	5b	Registration on PROSPERO (preferable)	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	Yes
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Yes
Search	8	Present a full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Yes
Study selection	9	State the process for selecting studies (i.e., screening, eligibility–inclusion/exclusion criteria, included in a systematic review, and, if applicable, included in the meta-analysis)	Yes
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Yes
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used in any data synthesis	Yes
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	Yes
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis (only for meta-analysis study)	Yes
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	Yes
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. (only for meta-analysis study)	No
Results			
Study selection	17	Give the number of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Yes
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Yes
Risk of bias within studies	19	Present data on the risk of bias of each study and, if available, any outcome level assessment (see item 12) (only for meta-analysis study)	Yes
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group, (b) effect estimates and confidence intervals, ideally with a forest plot (only for meta-analysis study)	Yes
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency (only for meta-analysis study)	Yes
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15) (only if meta-analysis was performed)	Yes
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). (only for meta-analysis study)	No
Discussion			
Summary of evidence	24a	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers)	Yes
	24b	Reporting the conflicting findings (from literature) and putting forth new ideas and/or new research directions	Yes
Limitations	25	Discuss limitations at the study and outcome level (e.g., risk of bias) and at the review-level (e.g., incomplete retrieval of identified research, reporting bias)	Yes
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	Yes
Citations	27	To cite from recent literature in the articles	Yes
Funding			
Funding	28	Describe sources of funding for the systematic review and other support (e.g., supply of data); the role of funders for the systematic review and the grant number	Yes

Supplementary Table S2: Search details from PubMed database

Serial no	Authors	Title of the publication	Publication type	Year of the publication	Included/ excluded	Reasons for exclusion
1	Ring JD, Lwin AA, Köhler TS	Current medical management of endocrine-related male infertility	Review	2016	Excluded	Publication type
2	Alder NJ, Keihani S, Stoddard GJ, Myers JB, Hotaling JM	Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hyperandrogenic subfertile men	Article	2018	Included	
3	Wenker EP, Dupree JM, Langille GM, Kovac J, Ramasamy R, Lamb D, Mills JN, Lipshultz LI	The use of HCG-based combination therapy for recovery of spermatogenesis after testosterone use	Article	2015	Excluded	Outcome
4	Chandrapal JC, Nielson S, Patel DP, Zhang C, Presson AP, Brant WO, Myers JB, Hotaling JM	Characterising the safety of clomiphene citrate in male patients through prostate-specific antigen, haematocrit, and testosterone levels	Article	2016	Excluded	Outcome
5	Chehab M, Madala A, Trussell JC.	On-label and off-label drugs used in the treatment of male infertility	Review	2015	Excluded	Publication type
6	Keihani S, Alder NJ, Cheng PJ, Stoddard GJ, Pastuszak AW, Hotaling JM	Obesity and baseline estradiol levels are independent predictors for initiation of anastrozole in hypogonadal men on clomiphene citrate	Article	2020	Included	
7	Niederberger C	Re: Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hypoandrogenic subfertile men	Article	2019	Excluded	Duplicate
8	Hsieh A, DiGiorgio L, Fakunle M, Sadeghi-Nejad H.	Management strategies in opioid abuse and sexual dysfunction: a review of opioid-induced androgen deficiency	Review	2018	Excluded	Publication type
9	Shoshany O, Abhyankar N, Mufarreh N, Daniel G, Niederberger C.	Outcomes of anastrozole in oligozoospermic hyperandrogenic subfertile men	Article	2017	Excluded	Intervention
10	Kim ED	Editorial Comment on "A Randomized Prospective Double-Blind Comparison Trial of Clomiphene Citrate and Anastrozole in Raising Testosterone in Hypogonadal Infertile Men"—New Comparative Insight on Alternative Therapies for Low Testosterone in Subfertile Men	Editorial comment	2015	Excluded	Publication type
11	Helo S, Ellen J, Mechlin C, Feustel P, Grossman M, Ditkoff E, McCullough A	A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men	Article	2015	Excluded	Intervention
12	Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES Jr.	Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association	Article	2012	Excluded	Intervention
13	Kacker R, Conners W, Zade J, Morgentaler A.	Bone mineral density and response to treatment in men younger than 50 years with testosterone deficiency and sexual dysfunction or infertility	Article	2014	Excluded	Outcome
14	Niederberger C.	Re: A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men	Article	2016	Excluded	Duplicate

Supplementary Table S2: Continued

Serial no	Authors	Title of the publication	Publication type	Year of the publication	Included/ excluded	Reasons for exclusion
15	Keihani, S; Alder, NJ; Cheng, PJ; Stoddard, GJ; Pastuszak, AW; Hotaling, JM	Obesity and baseline estradiol levels are independent predictors for initiation of anastrozole in hypogonadal men on clomiphene citrate	Article	2020	Included	Duplicate
16	Krzastek, SC; Sharma, D; Abdullah, N; Sultan, M; Machen, GL; Wenzel, JL; Ells, A; Chen, XZ; Kavoussi, M; Costabile, RA; Smith, RP; Kavoussi, PK	Long-term safety and efficacy of clomiphene citrate for the treatment of hypogonadism	Article	2019	Excluded	Intervention
17	Alder, NJ; Keihani, S; Stoddard, GJ; Myers, JB; Hotaling, JM	Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hyperandrogenic subfertile men	Article	2018	Included	Duplicate
18	Shoshany, O; Abhyankar, N; Mufarreh, N; Daniel, G; Niederberger, C	Outcomes of anastrozole in oligozoospermic hyperandrogenic subfertile men	Article	2017	Excluded	Intervention
19	Chandrapal, JC; Nielson, S; Patel, DP; Zhang, C; Presson, AP; Brant, WO; Myers, JB; Hotaling, JM	Characterising the safety of clomiphene citrate in male patients through prostate-specific antigen, haematocrit, and testosterone levels	Article	2016	Excluded	Duplicate
20	Helo, S; Ellen, J; Mechlin, C; Feustel, P; Grossman, M; Ditkoff, E; McCullough, A	A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men	Article	2015	Excluded	Duplicate
21	Wenker, EP; Dupree, JM; Langille, GM; Kovac, J; Ramasamy, R; Lamb, D; Mills, JN; Lipshultz, LI	The use of HCG-based combination therapy for recovery of spermatogenesis after testosterone use	Article	2015	Excluded	Duplicate
22	Chehab, M; Madala, A; Trussell, JC	On-label and off-label drugs used in the treatment of male infertility	Article	2015	Excluded	Duplicate
23	Gudeloglu, A; Brahmbhatt, JV; Parekattil, SJ	Medical management of male infertility in the absence of a specific etiology	Review	2014	Excluded	Publication type
24	Trost, LW; Khera, M	Alternative treatment modalities for the hypogonadal patient	Review	2014	Excluded	Publication type
25	Ko, EY; Siddiqi, K; Brannigan, RE; Sabanegh, ES	Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association	Article	2012	Excluded	Duplicate
26	S Helo, J Ellen, C Mechlin, P Feustel, M Grossman, E Ditkoff, A Mccullough	A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men	Article	2015	Excluded	Comparator
27	S Helo, C Mechlin, A Alkaram, A McCullough	Clomiphene citrate is superior to anastrozole in raising testosterone in hypogonadal infertile men: a prospective randomized double blind comparison trial	Article	2018	Excluded	Study design
28		The effects of natesto for treatment of hypogonadism	Clinical trial	2021	Excluded	Intervention
29		Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination	Clinical trial	2010	Excluded	Intervention

Supplementary Table S2: Continued

Serial no	Authors	Title of the publication	Publication type	Year of the publication	Included/ excluded	Reasons for exclusion
30	ED Kim	Editorial Comment on "A Randomized Prospective Double-Blind Comparison Trial of Clomiphene Citrate and Anastrozole in Raising Testosterone in Hypogonadal Infertile Men"-New Comparative Insight on Alternative Therapies for Low Testosterone in Subfertile Men	Article	2016	Excluded	Duplicate
31	A McCullough, R Xu, S Helo, L Elebyjian, P Feustel	The effect of testosterone restorative therapy (TRES) on testicular volume. Results from a double blind randomized 12 week trial of clomiphene citrate vs anastrozole	Article	2018	Excluded	Publication type
32	Julie Brown, Cindy Farquhar	Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome	Article	2016	Excluded	Population
33	Sebastian Franik, Stephanie M Eltrop, Jan AM Kremer, Ludwig Kiesel, Cindy Farquhar	Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome	Article	2018	Excluded	Population
34	Reuben Olugbenga Ayeleke, Joyce Danielle Asseler, Ben J Cohlen, Susanne M Veltman-Verhulst	Intra-uterine insemination for unexplained subfertility	Article	2020	Excluded	Population
35	Rui Wang, Nora A Danhof, Raissa I Tjon-Kon-Fat, Marinus JC Eijkemans, Patrick MM Bossuyt, Monique H Mochtar, Fulco van der Veen, Siladitya Bhattacharya, Ben Willem J Mol, Madelon van Wely	Interventions for unexplained infertility: a systematic review and network meta-analysis	Article	2020	Excluded	Study design
36		Anastrazole and clomiphene to evaluate hypogonadal symptoms and erectile function	Clinical trial (NCT03933618)	2019	Excluded	Comparator
37		Microenvironment and male fertility	Clinical trial (NCT04704141)	2021	Excluded	Intervention

Supplementary Table S3: Risk of bias–Newcastle–Ottawa questions for assessing the quality of cohort study

Study ID	Item	Authors judgment	Risk of bias
Keihani *et al.*, 2020[16]	**Patient selection** Representativeness of the exposed cohort	Truly representative of hypogonadal men treated with CC in a single fertility center*	****
	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort*	
	Ascertainment of exposure	Secure records and structured interview*	
	Demonstration outcome of interest was not present at the start of the study	Yes, Patients with a history of sex chromosome disorders, (2) recent treatment with exogenous testosterone or hormonal therapy, and (3) lack of follow-up after CC initiation were excluded*	
	Comparability		
	Comparability of cohorts based on the design or analysis	Yes. Combination therapy*	*
	Outcome		
	Assessment of outcome	Record linkage*	***
	Was follow-up long enough for outcomes to occur	Yes*	
	Adequacy of follow-up of cohorts	All patients were followed for 24 months*	

CC, Clomiphene citrate
The star system was used for assessing the parameters like selection, comparability, and outcome

Supplementary Table S4: Risk of bias–Moga tools for assessing the quality of case series studies

Study ID	Source of bias	Authors judgment
Alder *et al.*, 2018[15]	Is the hypothesis/aim/objective of the study clearly stated?	Yes
	Are the characteristics of the participants included in the study described?	Yes
	Were the cases collected in more than one center?	No
	Are the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?	Yes
	Were the participants recruited consecutively?	Yes
	Did the participants enter the study at a similar point in the disease?	Yes
	Was the intervention of interest clearly described?	Yes
	Were additional interventions (cointerventions) reported in the study?	Yes
	Are the outcome measures established a priori?	Yes
	Were the relevant outcomes measured with appropriate objective and/or subjective methods?	Yes
	Were the relevant outcomes measured before and after the intervention?	Yes
	Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
	Was the length of follow-up reported?	Yes
	Was the loss to follow-up reported?	No
	Does the study provided estimates of the random variability in the data analysis of relevant outcomes?	Yes
	Are the adverse events related with the intervention reported?	Yes
	Are the conclusions of the study supported by results?	Yes
	Are both competing interests and sources of support for the study reported?	No

Review Article

The evolution of Alzheimer's disease therapies: A comprehensive review

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Abstract

Alzheimer`s disease (AD) is a progressive neurodegenerative disease which accounts for most of the cases of dementia. The progression of the disease cannot be fully controlled by current medications, nor do they produce adequate therapeutic results. Understanding the molecular and cellular alterations linked to AD pathogenesis has advanced significantly in recent decades. Amyloid-peptide-containing cerebral plaques and thread-like neuronal structures made of the microtubule-associated protein TAU are two pathogenic features of the condition. Therefore, inhibiting amyloid formation, aggregation, or subsequent neurotoxic events is the primary goal of therapeutic drug development. Here, some newer therapeutic modalities are described, including anti-amyloid therapy, anti-tau therapy, antineuroinflammatory therapy, neuroprotective agents including *N*-methyl-d-aspartate (NMDA) receptor modulators, and brain stimulation. Drug repositioning may speed up the development of pharmaceuticals, but non-pharmacological therapies, particularly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), also have the potential to be used in therapeutic settings. Here we discussed current symptomatic therapy for AD as well as novel prospective disease-modifying medicines that are presently being investigated in phase I–III trials in this review. The study emphasizes how taking into account the intricate nature of AD pathogenesis and investigating drug repurposing strategies which can open the door to the creation of innovative AD therapies.

Keywords: Alzheimer's disease, amyloid plaques, dementia, neurodegenerative, neurofibrillary tangles

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease. Over 26 million people worldwide are affected by Alzheimer's disease (AD), the most common neurological disease of aging, and this number is steadily rising.[1] Only after cardiovascular, cerebrovascular illnesses, and malignant tumors, Alzheimer's disease becomes the third greatest cause of disability and death for the aged.[2] This review aims to provide a comprehensive overview of the field, offer insights into treatment effectiveness, and guide future research and clinical practice in the quest to better understand and manage Alzheimer's disease.

Clinically, Alzheimer's disease is indicated by a slow and steady decline in cognitive function, and neuropathologically, the condition is indicated by the presence of neuropil threads, loss of specific neurons, and loss of synapses in

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addition to the classic signs of neurofibrillary tangles and senile plaques.[3-5]

AD is a form of progressive dementia without a recognized cause or known treatment. Over 100,000 fatalities are attributed to AD each year in the United States, where it accounts for about 60% of all dementia cases in adults over 65 years. Due to the disease's terrible consequences on the patient with AD cognitive, emotional, and physical function has a very bad impact on both the patient and their families.[6,7]

Several cutting-edge medications are now being investigated for the treatment of Alzheimer's disease. Clinical trials for a few of these treatments are now being conducted, and preliminary results are promising. One such treatment is vaccination which specifically targets amyloid-beta, a protein that builds up in the brain of patients with Alzheimer's disease and is thought to speed up the disease's course. additional treatments that are currently being investigated include medications that target tau, another protein found in the brain of people with Alzheimer's disease, as well as techniques designed to promote the creation of new neurons in the brain.[8,9]

Another technique for treating Alzheimer's disease is through stem cell therapies, which work to replace or repair damaged brain cells. Genetic modalities for the treatment of Alzheimer's disease are also a newer concern of research.[10,11]

PATHOPHYSIOLOGY

AD has multiple etiologies and is a complicated disease. A majority of instances of the uncommon form of AD known as early-onset AD, which has mutations in the presenilins 1 and 2 and the amyloid precursor protein (APP), follow an autosomal-dominant pattern.[3,12,13] The significance of genetics in Alzheimer's disease has grown in prominence following Genome-Wide Association Studies (GWAS), which have unveiled a multitude of genetic variations linked to the risk of the disease. Alzheimer's is a complex interplay of various factors involving the intricate association between amyloid and tau proteins. The accumulation of amyloid-beta (Aβ) can trigger tau pathology, resulting in the development of neurofibrillary tangles. Amyloid plaques are aberrant protein buildups that harm and kill brain tissues. Tau protein gets twisted into neurofibrillary tangles, which build up inside brain cells and cause cell death. Amyloid plaques and neurofibrillary tangles are two important pathological lesions in the brain that are indicative of AD. Additionally, inflammation plays a central role, with microglia reacting to Aβ plaques and contributing to neuroinflammation, potentially exacerbating the condition. Furthermore, impaired mechanisms for disposing of Aβ can lead to its accumulation within the brain. More recently, the role of astrocytes has gained recognition; these glial cells, typically engaged in supporting and maintaining neurons, can become reactive in Alzheimer's, participating in neuroinflammation and potentially impacting the progression of the disease.[14]

The hippocampus, amygdala, entorhinal cortex, cortical association areas of the frontal, temporal, and parietal cortices, as well as subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus, may all exhibit neuronal loss or disease.[15-17] The accumulation of tau proteins is inversely correlated with hippocampal atrophy, cognitive decline, and brain atrophy. Alzheimer's disease causes the temporofrontal cortex atrophy and loss of neurons, which results in inflammation, the deposition of amyloid plaques, abnormal protein clusters, and tangled bundles of fibers. As a result, there is an increase in the number of monocytes and macrophages in the cerebral cortex, which also activates the microglial cells in the parenchyma.[15] The neuropathological hallmarks of Alzheimer's disease (AD) include "positive" lesions such as amyloid plaques, cerebral amyloid angiopathy, neurofibrillary tangles, a glial responses, and "negative" lesions such as neuronal and synaptic loss.[6,16,17]

Signs and symptoms

Alzheimer's disease (AD) is the most common subtype of dementia, making up around 60% of the entire dementia spectrum. Clinically, it is distinguished by a progressive loss of memory and orientation as well as other cognitive deficiencies, such as poor judgment and decision-making, apraxia, and language problems. These frequently come with a variety of neuropsychiatric symptoms (i.e., depression, apathy, anxiety, agitation, delusions, and hallucinations) [18].

Diagnosis

The diagnosis of Alzheimer's disease (AD) in its early, pre-clinical stage has undergone a remarkable transformation through the adoption of contemporary biomarker-driven techniques. These state-of-the-art diagnostic approaches center on identifying precise biological markers associated with AD's pathological processes, notably Aβ and tau proteins. These indicators can be identified in various ways, including through the examination of cerebrospinal fluid, blood samples, or advanced imaging methods such as positron emission tomography (PET) scans. In the present era, AD diagnosis heavily relies on two pivotal biomarkers: Aβ and tau protein.[18,19] A test to find a new sign of Alzheimer's

disease-related neurodegeneration in a blood sample has been created by a team of neuroscientists. The "brain-derived tau" biomarker, also called BD-tau, outperforms current blood diagnostic techniques. According to researchers, blood level monitoring may improve clinical trial design and expedite patient enrollment and screening.[20,21]

Management

It is important to remember that a lot of these treatments are still in the research and development phase [Figure 1], and it is not yet known if they will be successful in treating Alzheimer's disease. Drugs known as "disease-modifying" agents, which have the potential to stop or at least significantly alter the course of AD, are still the subject of intensive investigation. They can alter the pathogenic processes that lead to the development of extracellular amyloid plaques and intracellular neurofibrillary tangles, as well as inflammation, oxidative damage, and other clinical signs, to prevent the illness from progression.[18]

DISEASE-MODIFYING AGENTS

Pharmacological treatment for Alzheimer's disease has only palliative and minor short-term advantages. The US Food and Drug Administration (FDA) has only approved a small number of drugs to treat Alzheimer's disease. The cholinesterase inhibitors donepezil, rivastigmine, galantamine, and tacrine have been licensed for the treatment of Alzheimer's disease. These medications function by raising the levels of acetylcholine in the CNS, a neurotransmitter crucial for memory and thought. Memantine blocks the function of NMDA receptors, which are important in the transmission of neuronal signals and are licensed for the treatment of moderate to severe Alzheimer's disease.[21,22]

NEW CHOLINESTERASE INHIBITORS

A phenylcarbamate derivative of physostigmine called phenserin reduces beta-APP and reversibly inhibits Acetyl Cholinesterase Enzyme (AChE). It absorbs quickly and is less hazardous than tacrine or physostigmine. Only the 2'-methyl substitution of the phenylcarbamoyl moiety sets tolserin apart from phenserin [23]. Physostigmine and fenserin, which are structural counterparts of tolserine, have not been shown to have the same potency as tolserine in inhibiting human AChE. Tesofensin decreases the presynaptic absorption of the neurotransmitters serotonin, norepinephrine, and dopamine, according to both *in vitro* and *in vivo* investigations. The neurotransmitters acetylcholine, norepinephrine, and dopamine that are compromised in individuals with Alzheimer's disease are improved by this substance. Tesofensin, which is thought to be neuroprotective, was administered to mice, and the concentration of beta-amyloid was observed to decrease.[24]

Amyloid-beta (Aβ) aggregation inhibitors

Several natural compounds have inhibitory properties on Aβ aggregation. These compounds are small molecules and their steric bulk is insufficient to interfere with Aβ

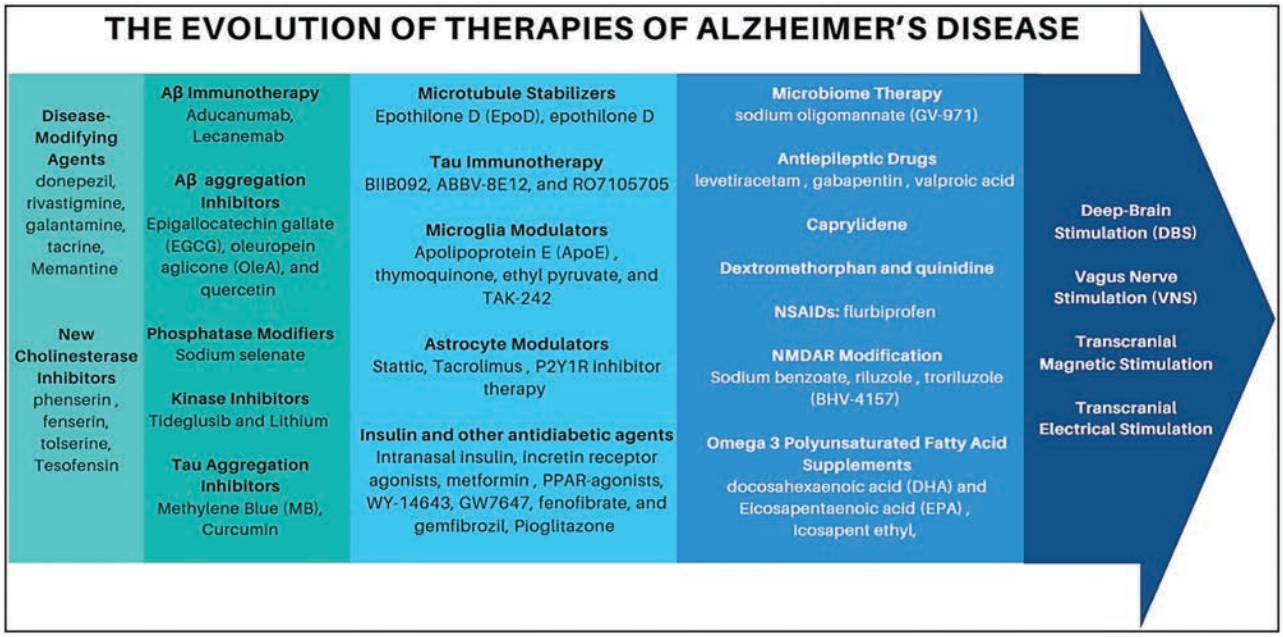

Figure 1: The evolution of therapies for Alzheimer's disease

aggregation. One strategy is to attack chaperone proteins in the brain, such as metals. Epigallocatechin gallate (EGCG), oleuropein aglicone (OleA), and quercetin are potential therapeutic agents in AD.[25,26]

Aβ immunotherapy

Aβ immunotherapy reduces the Aβ load either actively or inactively. Passive immunotherapy targets neurotoxic Aβ oligomers to aid in the clearance of Aβ. The US FDA authorized aducanumab to treat AD patients in June 2021.[27] Lecanemab decreased amyloid indicators in early Alzheimer's disease, and moderately slowed cognitive and functional decline compared to placebo after 18 months, however, it was also linked to negative side effects.[28]

PHOSPHATASE MODIFIERS

Phosphatase modifiers decrease phosphorylation by activating phosphatases, like Protein phosphatase 2A enzyme (PP2A). Sodium selenate, a PP2A activator, is essential for neurological functions. A phase II trial found no cognitive improvement in mild to moderate AD.[29] A super nutritional supplement increased selenium uptake, but had minor clinical efficacy.[30,31]

KINASE INHIBITORS

Kinase inhibitors reduce tau hyperphosphorylation and post-translational alterations. None of these medications have been tested in AD clinical trials. In AD, Tideglusib and Lithium have both been studied as Glycogen synthase kinase-3 (GSK-3) inhibitors. Further research is required to determine the effectiveness of these agents.[32,33]

TAU AGGREGATION INHIBITORS

A synthetic phenothiazine dye called methylene blue (MB) was the first inhibitor of tau aggregation. As a result, the use of MB in AD therapy is still debatable. Curcumin, a food additive and coloring agent that breaks down tau oligomers *in vitro* and decreases the development of tau sheets, prevents tau from aggregating. However, a protracted course of curcumin therapy did not stop the decline in cognitive function.[34,35]

MICROTUBULE STABILIZERS

Epothilone D (EpoD) is a microtubule stabilizer and antifungal drug. *In vitro*, epothilone D increases microtubule bundling and causes tubulin to polymerize into microtubules. *In vitro*, the activity-dependent neuroprotective protein (ADNP) derivative NAP (davunetide, CP201) guards against katanin disruption of microtubules. When given intravenously for 12 weeks to mild cognitive impairment (MCI) patients, NAP demonstrated cognitive and functional improvement in phase II double-blind RCT.[36-38]

TAU IMMUNOTHERAPY

Active tau vaccines have been developed to stimulate the production of anti-tau antibodies. In 12 weeks, ACI-35-treated tau transgenic mice showed a rapid immune response and a decline in phosphorylated tau. Passive immunotherapy is being developed for tau pathology. These include three humanized lgG4 monoclonal antibodies: BIIB092, ABBV-8E12, and RO7105705. Phase II double-blinded RCTs are still ongoing to assess the efficacy of ABBV-8E12 in the treatment of patients with early AD.[39-42]

MICROGLIA MODULATORS

Apolipoprotein E (ApoE) signaling pathways are linked to glial activation, which in turn activates the Triggering Receptor Expressed in Myeloid Cells 2 (TREM2), the Toll-like receptor (TLR), and the colony-stimulating factor-1 receptor (CSF1R).[43] ApoE and TREM2 mutations are regarded as significant risk factors for AD. The connection enhances TREM2-mediated apoptotic neuron phagocytosis. Increased TREM2 expression in 5xFAD mice improved memory function in a mouse model of AD.[44] Several TLR4 inhibitors, such as thymoquinone, ethyl pyruvate, and TAK-242, alleviated cognitive abnormalities in AD animal models. TLR2 binds to Aβ and facilitates microglia phagocytosis of Aβ.[45] Through inhibition or activation, TLR2 pathway dysregulation increased memory decline in AD mice. In animal models of AD, the CSF1R pathway promotes microglial growth. In P301S mice, JN-J527 treatment reduced tau-mediated neurodegeneration and functional impairment.[46]

ASTROCYTE MODULATORS

The calcineurin/Nuclear Factor of Activated T cells (calcineurin/NFAT), the nuclear factor-kB/nod-like receptor family pyrin domain containing 3 (NFB/NLRP3) mitogen-activated protein kinase (MAPK), and the P2Y1 purinoreceptor (P2Y1R) pathways are some of the signaling pathways involved in the astrocyte reaction in AD.[47] The intraperitoneal injection of Stattic, a specific STAT3 inhibitor, restored learning and memory impairment in 5XFAD mice.[48,49] The calcineurin/NFAT pathway encourages the generation of cytokines that cause inflammation. The calcineurin/NFAT pathway was blocked

by FK506 (Tacrolimus), which improved the cognitive deficit in APP/PS1 mice.[50,51] In animal studies of AD, MW181 and NJK14047, two highly specific p38 MAPK inhibitors, were examined. In aged hTau mice, MW181 reversed cognitive impairment by preventing tau phosphorylation. While NJK14047 improved cognitive abilities in 5XFAD mice, it also reduced amyloid deposition and cell death. P2Y1R inhibitor therapy reduced cognitive impairments and restored normal astrocyte activity in APPPS1 mice.[52,53]

Insulin and other antidiabetic agents

Intranasal insulin treatment reduced memory impairment in MCI and AD, according to a double-blinded RCT. In animal models of AD and Parkinson's disease, several incretin receptor agonists, including liraglutide, lixisenatide, exendin-4, semaglutide, peptides 17, 18, and 20, as well as DA-JC4 and DA-CIB, demonstrated a potential therapeutic impact.[54] Comparatively to the placebo group, the 12-month liraglutide treatment delayed cognitive deterioration in the treated group. Liraglutide is the subject of an additional phase II double-blind RCT being conducted in mild AD patients.[55] Daily doses of 500–2000 mg of metformin were given to the treatment group. When compared to the placebo group, the treated group displayed less recall memory deterioration after a 12-month intervention.[56] Four PPAR-agonists, WY-14643, GW7647, fenofibrate, and gemfibrozil, showed therapeutic potential in animal models of AD. Pioglitazone is a PPAR-agonist for treating diabetes. An open-label phase II RCT of pioglitazone showed cognitive benefits in diabetic patients.[57]

MICROBIOME THERAPY

By producing different neurotransmitters and neuromodulators, the gut microbiota's growth influences brain function and communication between the gut and the brain. Dysbiosis of the gut microbiota causes an excess of lipopolysaccharides to be produced there, which raises BBB permeability. A marine-derived oligosaccharide called sodium oligomannate (GV-971) inhibits gut microbiota dysbiosis, controls neuroinflammation, and weakens A-aggregates.[58,59]

ANTIEPILEPTIC DRUGS

A multicenter double-blinded phase III RCT of AGB101 (levetiracetam) in individuals with MCI is now being conducted to assess the drug's potential to halt cognitive and functional decline.[60] Treatment with gabapentin demonstrated a neuroprotective effect and reduced brain damage in a dose-dependent manner in cerebral ischemia-reperfusion rats.[61] Preliminary research suggested that gabapentin therapy may help to treat AD in dementia with behavioral and psychological symptoms (BPSD). The daily dosage of 200–3600 mg of gabapentin reduced agitation and enhanced cognition. The antiepileptic medication valproic acid may inhibit glycogen synthase kinase-3 (GSK-3) activity and microtubule dissociation.[62,63]

Caprylidene

Caprylidene is a medicinal food that is metabolized into ketone bodies, which the brain can utilize for energy when the metabolism of glucose is impeded, and it uses a completely different strategy to treat AD. The ability to absorb glucose is significantly reduced in aged and AD patients. For the treatment of AD and individuals with age-related cognitive impairment, caprylidene replenishes reduced glucose levels in the brain.[64,65]

Dextromethorphan and quinidine

Dextromethorphan and quinidine, a novel combination, were demonstrated to lessen emotional lability as seen by fewer episodes of sobbing or laughing in AD patients. Dextromethorphan, which is metabolized by CYP2D6, has higher bioavailability due to quinidine's inhibition of the CYP2D6 metabolic enzyme. Dextromethorphan blocks NMDA receptors (*N*-methyl-d-aspartate receptor) and reduces excitatory glutamate release by acting as an agonist at sigma-1 (1) receptors.[66,67]

NSAIDs

By blocking secretase enzymes, NSAIDs like flurbiprofen may reduce the formation of aggregates.[68]

N-methyl-d-aspartate receptor (NMDAR) modification

In the early stages of AD, increasing or decreasing NMDAR activity showed therapeutic promise. Sodium benzoate, a preservative, increases NMDAR activity by blocking D-amino acid oxidase (DAAO). In phase II double-blinded RCT, patients who received sodium benzoate treatment for 24 weeks and received doses ranging from 250 to 1500 mg/day exhibited both changed brain activity and cognitive benefit in MCI.[69] Benzoate therapy showed cognitive improvements in women with moderate to severe AD in a multicenter, double-blinded RCT.[70] A glutamate modulator, riluzole indirectly suppresses presynaptic glutamate release and modifies postsynaptic NMDAR activity. To evaluate the impact of riluzole on mild AD's cerebral metabolism and cognitive function, a phase II double-blinded RCT was conducted. A phase II double-blinded RCT of the riluzole derivative troriluzole (BHV-4157) is now being proposed to assess the cognitive change in patients with mild to moderate AD.[71-73]

Omega 3 polyunsaturated fatty acid supplements

Only combined Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) supplements, according to a recent systematic review and meta-analysis study, appeared to improve several elements of cognitive performance in AD patients. Icosapent ethyl, an ethyl ester of EPA, is currently the subject of a phase III RCT to assess its effects on cognition and the cerebrum in cognitively healthy adults who are at higher risk of AD.[74,75]

Deep-brain stimulation (DBS)

In 2010, six individuals with moderate AD participated in a small-scale phase I DBS experiment. Following a continuous stimulation regimen of 12 months, the patients displayed less cognitive deterioration and better glucose metabolism in the temporoparietal lobe.[76] In moderate AD patients, a phase II double-blinded RCT of fornical DBS was conducted. After 12 months of fornical DBS treatment, a subgroup study revealed that patients ≥65 years or older had marginally improved cognitive function whereas younger patients had worsened cognitive function.[77]

The nucleus basalis of Meynert (NBM), in addition to the fornix, is regarded as a targeted area of DBS. NBM-DBS was tested in a small-scale, double-blinded, sham-controlled phase I experiment on mild to moderate AD patients. Two-thirds of the patients had improved or stabilized cognitive performance at the 12-month follow-up evaluation.[78]

Vagus nerve stimulation (VNS)

There are two types of vagus nerve stimulation: invasive and noninvasive. A brief 6-month iVNS pilot trial was conducted in AD patients in 2002. Approximately 70% of patients displayed stabilized or enhanced cognitive performance after 12-month iVNS treatment.[79] Double-blinded, sham-controlled crossover research is being conducted to assess the therapeutic value of nVNS for MCI patients.[80]

Transcranial magnetic stimulation (TMS)

For 4 weeks, mild to moderate AD patients receiving cognitive training got either real or fake repetitive Transcranial Magnetic Stimulation (rTMS) treatment. Patients receiving high-frequency rTMS demonstrated cognitive and functional improvement in mild to moderate AD when compared to the sham group after 5 days of stimulation.[81] In a different trial, patients with MCI and mild to moderate AD were given high-frequency rTMS to observe any effect. Greater clinical improvements in episodic memory were seen in the treated group compared to the sham group following left parietal lobe stimulation, but the impact was not seen in other cognitive domains. The outcome demonstrated that rTMS provided benefits in the treatment of mild AD, with better memory and language.[82,83]

Transcranial electrical stimulation (TES)

In 2009, individuals with mild to moderate AD were examined using anodal Transcranial Direct Current Stimulation (tDCS) at the left parietal region. In one study, patients with mild to moderate AD evaluated the effects of 2 mA anodal tDCS across the left temporal region. Patients with moderate AD were the first to be examined with the 1.5 mA tDCS technique of the bilateral temporoparietal area in 2008. Each genuine treatment lasted for 15 min, but a sham stimulation only lasted for 10 s.[84]

Cognitive stimulation therapy (CST)

Cognitive stimulation therapy (CST) is a structured and research-backed strategy that holds promise for boosting cognitive and social capabilities in Alzheimer's disease patients. The primary goal of CST is to create a supportive and stimulating atmosphere that fosters social interaction and cognitive involvement, ultimately seeking to enhance the overall well-being and quality of life for those with Alzheimer's disease. CST entails involving participants in a sequence of themed activities and discussions crafted to activate various cognitive functions, such as memory, attention, and problem-solving. These tasks typically take place in group settings and are customized to match each individual's cognitive abilities and preferences. Research findings have suggested that CST can yield favorable results, including improved cognitive abilities, elevated mood, and increased social engagement, positioning it as a valuable non-pharmacological approach in Alzheimer's disease management.[85]

CONCLUSION

This comprehensive review stands as a crucial and indispensable asset in our continuous efforts to combat the profound neurodegenerative condition of Alzheimer's disease. It offers a profound insight into the ever-evolving realm of Alzheimer's disease treatments, spotlighting the advancements achieved in comprehending its origins and the development of therapeutic strategies throughout the years. Spanning from the historical context to the intricate interplay of amyloid and tau, the influence of genetics, the role of inflammation, and the malfunction in amyloid clearance, this review has provided a holistic perspective on the multifaceted nature of Alzheimer's disease. Furthermore, it has brought attention to the emerging significance of astrocytes in the disease's progression.

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Review Article

Efficacy of angiotensin receptor blockers for erectile dysfunction in hypertensive men: A systematic review

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Abstract

Erectile dysfunction (ED) is a condition that affects many men, especially as they age, and is an indicator of an underlying health condition and is a risk factor for cardiovascular disease. ED also causes significant psychological distress due to stress, anxiety, and low self-esteem related to reduced sexual activity and satisfaction. A high incidence of ED is known to be associated with men with hypertension and diabetes. Angiotensin receptor blockers (ARBs) are newer-generation antihypertensive drugs elucidating a beneficial effect on erectile function compared to older-generation drugs. This study aimed to systematically review the literature to investigate the efficacy of ARBs compared to other classes of antihypertensive drugs in improving ED-related outcomes. A literature search was carried out in Medline, Embase, the Cochrane Library databases, and other relevant sources to select clinical studies that compared the efficacy of ARBs with other antihypertensive drugs in men with concomitant hypertension and ED. Overall, twelve clinical studies comprising 11,672 hypertensive patients with ED were included. Analyses of the outcomes show that ARBs significantly reduce arterial pressure and improve erectile function, frequency of sexual activity, and overall satisfaction in patients. ARBs depress the process of oxidative stress and thus increase sexual desire among the patients with ED patients. Both monotherapy and combination therapies are beneficial for improving erectile function and compliance among patients.

Keywords: Angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, erectile dysfunction, hypertension

Key Messages: Angiotensin receptor blockers (ARBs) inhibit the oxidative stress process while increasing sexual desire in patients with hypertension. Their neutral effect on levels of serum testosterone and sex hormone-binding globulin makes them an ideal choice for hypertensive patients with lower androgen levels. Both monotherapy and combination therapies with ARBs can be effective in improving erectile function and compliance.

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INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or sustain an erection sufficient for satisfactory sexual performance. ED is caused by vascular endothelial dysfunction in cavernosal vessels, which reduces blood flow to the muscles involved in erectile function.[1,2] Physiological (organic) and psychological factors are the most common causes of ED. Globally, more than 152 million men suffered from ED in 1995, and the number of those affected is expected to rise to 322 million by 2025.[3] The prevalence of ED differs with age, ranging from 5.1% in men aged 20–39 years to 70.2% in men aged 70 years and older.[4]

Patients with ED have a significantly lower quality of life due to the psychological burden encompassing low levels of sexual activity, sexual desire, and sexual satisfaction.[5] In addition, ED is also associated with cardiovascular (CV) risk factors and CV diseases.[6] ED is strongly associated with hypertension[7] due to the existence of the renin-angiotensin system in the penis.[8] Higher levels of angiotensin II are produced due to hyperactivity of the renin-angiotensin system in patients with hypertension. This in turn stimulates the release of free radicals in the endothelium and consequent oxidative stress in cavernosal vessels, resulting in ED.[9] From a therapeutic point of view, in hypertension, reduced angiotensin II synthesis and inhibition of its activities in cavernosum vessels aid erectile function.[10] The administration of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) strongly inhibits the synthesis and actions of angiotensin II in renin–angiotensin system.[11]

According to ONTARGET/TRANSCEND trials, ACEIs and ARBs displayed similar effects on ED. The findings of the trials also showed that both ARBs and ACEIs are associated with improved sexual function, sexual satisfaction, and associated CV outcomes.[6] However, other anti-hypertension drugs (diuretics, β-blockers, and calcium channel blockers) are associated with a higher incidence of ED. Diuretics and β-blockers have a significant association with ED by reducing penile blood flow, whereas calcium channel blockers rarely cause ED. In males with hypertension, medically induced ED can increase non-adherence to therapy and treatment discontinuation.[12-15]

However, clinical data on the comparative efficacy of ARBs and other drugs in treating ED among men with hypertension has not been systematically reviewed and studied, and this information is relevant and important in finding the optimal treatment for both conditions. In this context, the present study was conducted with the aim of systematically identifying the studies and comparing the ED outcomes of different ARBs and other classes of antihypertensive drugs (calcium channel blockers, diuretics, and β-blockers) in hypertensive men. The findings of this systematic literature review will also be helpful in identifying the gaps and limitations in the current evidence and provide directions for future research.

MATERIALS AND METHODS

Literature search

The present study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] The search was restricted to studies published between 2001 and 2022 and conducted using electronic databases such as PubMed/Medline, Embase, National Institute of Health (https://clinicaltrials.gov/), and the Cochrane Central Register of Controlled Trials using MeSH terms/Emtree (for EMBASE)/ such as "ARBs" AND "ED", "ARBs" AND "Sexual dysfunction". To collect additional information, a manual search of other bibliographies and relevant review articles was conducted. The complete search strategy has been provided in Table 1.

Table 1: Search strategy for the electronic databases

Database	Search strategy	Hits
PubMed	((Azilsartan OR Edarbi OR Candesartan OR Atacand OR Eprosartan OR Irbesartan OR Avapro OR Losartan OR Cozaar OR Olmesartan OR Benicar OR Telmisartan OR Micardis OR Valsartan OR Diovan) OR (Antagonists, Angiotensin Receptor OR Angiotensin Receptor Blocker* OR Angiotensin II Receptor Antagonists OR Angiotensin II Receptor Blockers)) AND (Erectile Dysfunction OR Male Sexual Impotence OR Male Impotence OR Impotence)	14
Embase	((azilsartan:ti,ab,kw OR edarbi:ti,ab,kw OR candesartan:ti,ab,kw OR atacand:ti,ab,kw OR eprosartan:ti,ab,kw OR irbesartan:ti,ab,kw OR avapro:ti,ab,kw OR losartan:ti,ab,kw OR cozaar:ti,ab,kw OR olmesartan:ti,ab,kw OR benicar:ti,ab,kw OR telmisartan:ti,ab,kw OR micardis:ti,ab,kw OR valsartan:ti,ab,kw OR diovan:ti,ab,kw) OR 'angiotensin receptor antagonist':ti,ab,kw) AND ('erectile dysfunction':ti,ab,kw OR 'male sexual impotence':ti,ab,kw OR impotence:ti,ab,kw) AND [english]/lim AND [clinical study]/lim	30
NIH (Clinical trials registry)	Erectile Dysfunction Azilsartan OR Candesartan OR Eprosartan OR Irbesartan OR Losartan OR Olmesartan OR Telmisartan OR Valsartan OR Angiotensin II Receptor Antagonists OR Angiotensin II Receptor Blockers	02
CENTRAL	Antagonists, Angiotensin Receptor OR Angiotensin Receptor Blocker* OR Angiotensin II Receptor Antagonists OR Angiotensin II Receptor Blockers OR Azilsartan OR Edarbi OR Candesartan OR Atacand OR Eprosartan OR Irbesartan OR Avapro OR Losartan OR Cozaar OR Olmesartan OR Benicar OR Telmisartan OR Micardis OR Valsartan OR Diovan AND MeSH descriptor: [Erectile Dysfunction] explode all trees	07
Total		53

Eligibility criteria

Studies were selected based on compliance with pre-defined inclusion and exclusion criteria. The eligibility criteria for inclusion were: (i) male patients (≥18 years) with concomitant hypertension and ED; (ii) randomized clinical trials, parallel-group assignment of observational studies, cross-over studies, controlled before and after studies, prospective studies; (iii) at least one treatment arm with ARBs (alone or combination with other antihypertensives); (iv) reported at least one of the pre-specified efficacy outcomes; (v) studies in the English language.

Studies on patients with ED not associated with hypertension (for example, ED due to chronic illness, injury, medications, neurological disorders, prostate/bladder/colon surgery, and Peyronie's disease), preclinical studies, retrospective analyses, conference abstracts, case reports, and consensus articles were excluded.

Outcomes

The efficacy of interventions was evaluated based on changes in (i) systolic blood pressure; (ii) diastolic blood pressure; (iii) International Index of Erectile Function-5 (IIEF-5) score (Erectile function, sexual desire, orgasmic function, sexual satisfaction, and overall satisfaction); (iv) self-administered questionnaire; (v) changes in sex hormone levels (testosterone [nmol]), sex hormone-binding globulin [nmol], 8-hydroxy-deoxyguanosine [nmol/l]), and Malondialdehyde (nmol/l); (vi) sexual activity (sexual intercourse episodes/week); (vii) CV events and CV-induced death.

Data extraction and analysis

The reviewers worked independently during the study selection and data extraction. All disagreements were resolved through discussion to obtain consensus. The following data were extracted from the included studies: (i) general information; (ii) study characteristics (study design, number of participants involved in the study); (iii) baseline characteristics; (iv) intervention and comparator data; (v) outcome data and presented in Table 2. Meta-analysis was not conducted due to the presence of heterogeneity in the interventions, populations, and outcome measurement.

Quality assessment of included studies

The quality of the included studies was appraised by the independent reviewers using the Cochrane risk of bias tool.[17] The following parameters were analyzed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting, to evaluate the impact of these studies on the overall results.

RESULTS

Literature search

A total of 53 studies were retrieved from the electronic databases published between 2001 and 2022. Of these, 39 studies at the abstract level and two studies at the full-text level were excluded. A total of 12 studies that met the inclusion criteria were included for the synthesis and systematic review. The flow diagram that detailed the search procedure is presented in Figure 1.

Characteristics of included studies

The detailed characteristics of the eligible studies are described in Table 2. Of the included studies, the majority were prospective studies ($N = 7$), followed by randomized controlled trials ($N = 3$), retrospective ($N = 1$) and cross-sectional studies ($N = 1$). All the studies analyzed the effect of ARBs on hypertensive patients with ED, including a total of 11,672 participants. The mean age of patients enrolled in the studies was 54.4 (range of 44.5–64.5) years. Patients had a mean baseline systolic and diastolic blood pressures of 127.2 mm Hg and 98.7 mm Hg, respectively. The mean lowest and highest IIEF-5 scores were 16 and 33, respectively. The total duration of the studies was 828 weeks (mean duration, 69 [range: 12 to 302] weeks), with the shortest duration of 12 weeks[18,19] and the longest duration being 302 weeks.[20] The baseline characteristics of the included studies are presented in Table 2 and Figure 1. Table 3 summarizes the main findings of the studies that were included in this review.

Study intervention

All the included studies compared ARB interventions either as monotherapy and or in combination therapy with other antihypertensives such as atenolol, irbesartan, losartan, valsartan, telmisartan, and candesartan as monotherapy and or in combination therapy were investigated to determine their effect on erectile function. Felodipine, metoprolol, hydrochlorothiazide (HCTZ), and rosuvastatin belonging to other classes of antihypertensives were combined with the interventions in the included studies. At least one of the pre-specified outcomes was analyzed in patients with hypertension and ED in all included studies.

Effect of ARBs on systolic blood pressure in patients with ED

Ten included studies evaluated the effect of ARBs on systolic blood pressure in patients with hypertension and ED which showed comparable results.[6,18-26]

A significant reduction in systolic blood pressure was observed in patients treated with irbesartan + HCTZ

Table 2: Study characteristic table of the included studies

Author, Year; Country	Study design	Study setting; Study period	Sample size;Age (Mean ± SD) years	Intervention	Control	Duration of hypertension	Outcomes assessed	Results
Llisterri, 2001;[18] USA, Spain	Prospective interventional study	Primary care clinics; 12 weeks	164; 47.4	Losartan with ED (*n* = 82)	Losartan without ED (*n* = 82)	<1 year: 37 1–3 years: 67 >3 years: 60	SBP, DBP	• SBP and DBP at baseline in the intervention group (153 ± 13/89 ± 8 mm Hg) and control group (155 ± 12/89 ± 8 mm Hg) • Reduction in SBP and DBP were similar in the intervention group (139 ± 7/83 ± 5 mm Hg) compared with control group 141 ± 10/81 ± 6 mm Hg) post 12 weeks of treatment ($P > 0.05$) • Losartan treatment improved sexual satisfaction from an initial 7.3% to 58.5% (x^2; $P = 0.001$)
Fogari, 2002;[21] Italy	RCT	Department of Internal Medicine and Therapeutics; 16 weeks	110; 44.5	Valsartan (*n* = 55) Atenolol (*n* = 55)	4 weeks run-in period on placebo	Naïve hypertension patients	SBP, DBP	• Baseline: ○ SBP: Atenolol (164 ± 12); Valsartan (164 ± 13) ○ DBP: Atenolol (102 ± 6); Valsartan (103 ± 6) • SBP and DBP decreased after 16 weeks (−20 ± 15 mm Hg and −19 ± 13 mm Hg, respectively) in both the treatment groups • Atenolol significantly reduced sexual activity (from 6.0 to 4.2 sexual intercourse episodes/month, $P < 0.01$ vs. placebo) • Valsartan increased sexual activity (from 5.8 to 7.4 sexual intercourse episodes/month, $P = 0.058$ vs. placebo)
Chiesa, 2003;[22] Switzerland	Prospective study	Swiss Cardiovascular Center, University Hospital, Bern, Switzerland; 16 weeks	2202; 54 ± 8	Valsartan (*n* = 1899)	Valsartan + HCTZ (*n* = 276), conventional treatment (*n* = 27)	NR	SBP, DBP	• Significant reduction in SBP (mean −18.6 mm Hg) and DBP (mean −11.6 mm Hg) $P < 0.0001$ vs. baseline • Sexual activity increased in valsartan group from 1.0 to 1.6 times during follow-up ($P < 0.0001$) • Similarly, in combination group sexual activity increased from 0.9 to 1.3 times during follow-up ($P < 0.0001$)
Dusing, 2003;[23] Germany	Prospective study	German Internal Medicine and General Medicine Practices; 26 weeks	3502; 55.8 ± 8.4	Valsartan monotherapy (*n* = 2064)	Combination therapy (*n* = 1438)	4.4 years	SBP, DBP, IIEF-5 score	• BP decreased from 158/94 mm Hg to 136/82 mm Hg during the 6 months of treatment ($P < 0.001$) • Significant increase in erectile function from 16.54 ± 8.27 to 23.14 ± 6.49 IIEF units ($P < 0.0001$) • Valsartan therapy markedly reduced ED in patients with both hypertensive treatment and without hypertensive treatment ($P < 0.0001$)
Baumhäkel, 2008;[24] Germany	Prospective study	NA; 24 weeks	1069; 59.3 ± 9.5	Irbesartan (*n* = 381)	Irbesartan with HCTZ (*n* = 673)	5.0 years	SBP, DBP, IIEF-5 score	• Irbesartan + HCTZ showed greater reduction in SBP (−25 ± 14 mm Hg) compared to Irbesartan alone (−22 ± 14 mm Hg), $P < 0.001$ • DBP did not differ significantly ($P = 0.08$) • One-third patients treated with irbesartan alone and in combination with HCTZ, post 6 months showed significant increase in sexual encounters ($P < 0.0001$)
Bohm, 2010;[6] United States, South America, Europe, Canada, Asia, South Africa, United Kingdom	RCT	732 study location; 104 weeks	1549; 64.7 ± 6.3	Ramipril (*n* = 400), Telmisartan (*n* = 395), Ramipril + Telmisartan (*n* = 381)	Placebo (*n* = 202)	NR	SBP, DBP, IIEF-5 score	• ED was predictive of all-cause death (HR: 1.84, 95% CI, 1.21 to 2.81, $P = 0.005$) • IIEF scores showed a high prevalence of mild to moderate, moderate, or severe ED at baseline

Table 2: Continued

Author, Year; Country	Study design	Study setting; Study period	Sample size;Age (Mean ± SD) years	Intervention	Control	Duration of hypertension	Outcomes assessed	Results
Yu, 2010;[26] China	Prospective study	The Second Hospital of Lanzhou University, China; 52 weeks	167; 41.5	Felodipine + Irbesartan (*n* = NR)	Felodipine + Metoprolol (*n* = NR) Irbesartan + Metoprolol (*n* = NR) Irbesartan + Hydrochlorothiazide (*n* = NR)	NR	BP, IIEF-5 score	• Effective BP lowering among all four treatment group: Felodipine + Irbesartan, Felodipine + Metoprolol, Irbesartan + Metoprolol and Irbesartan + Hydrochlorothiazide ($P < 0.01$) and no difference in the group ($P > 0.05$)
Segal, 2011;[27] USA	Retrospective cohort study	The James Buchanan Brady Urological Institute, USA; 104 weeks	29; 58.4 ± 1.2	Irbesartan (*n* = 17)	Without Irbesartan (*n* = 12)	NR	IIEF-5 score	• IIEF-5 scores at 24 months after surgery were statistically similar between the two groups (control = 15.2 ± 2.0; irbesartan = 14.1 ± 3.1; $P = 0.77$)
Chen, 2012;[19] China, USA	Prospective study	NA; 12 weeks	124; 48.1 ± 12.6	Losartan (*n* = 32)	Control (*n* = 30) Tadalafil (*n* = 31) Losartan + Tadalafil (*n* = 31)	NR	SBP, DBP, IIEF-5 score	• IIEF-5 scores were significantly improved with the treatment: ○Tadalafil vs. baseline (9.40 ± 3.66 vs. 16.00 ± 4.55) ○ Losartan vs. baseline (9.68 ± 3.46 vs. 13.28 ± 4.92) ○ Losartan + tadalafil vs. baseline (9.94 ± 4.02 vs. 18.61 ± 4.83) ($P < 0.05$) as compared with baseline
Yang, 2013;[25] China	Prospective study	Lanzhou University Second Hospital in Lanzhou, China; 48 weeks	218; 46.9 ± 6.7	Felodipine + Irbesartan (*n* = 113)	Felodipine + Metoprolol (*n* = 105)	6.94 years	SBP, DBP, IIEF-5 score	• No significant difference in the prevalence of ED before and after treatment in either group ($P > 0.05$) • SBP and DBP decreased progressively in both the groups by 4th week and remained stable in both the groups through 48th week
Joseph, 2018;[20] Canada	RCT	Hamilton General Hospital, Canada; 302 weeks	2153; 61.5	Rosuvastatin (*n* = 1082), Candesartan + HCTZ (*n* = 1061)	Placebo (*n* = 1071), Placebo (*n* = 1092)	NR	SBP, IIEF-5 score	• Mean change in the IIEF-EF score did not differ with rosuvastatin compared with placebo (−1.4; standard error [SE], 0.3 vs. −1.5; SE, 0.3; $P = 0.74$) • Cand + HCTZ compared with placebo (−1.6; SE, 0.3 vs. −1.3; SE, 0.3; $P = 0.10$) • Combination therapy compared with double placebo ($P = 0.35$)
Correia, 2022;[28] Kenya	Descriptive cross-sectional study	KNH hospital, Kenya; 24 weeks	385; 56.2 ± 11.3	Alpha blockers (*n* = 18), ACEi (*n* = 118), ARB (*n* = 174), CCB (*n* = 238), β- blockers (*n* = 129)	NR	5.0 years	IIEF-5 score	• High prevalence of ED was observed • Most men had mild ED, with nearly one in ten having severe ED

ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, BP: blood pressure, CBA: controlled before and after, CCB: calcium channel blocker, CI: confidential interval, DBP: diastolic blood pressure, ED: erectile dysfunction, HCTZ: hydrochlorothiazide, HR: Hazard ratio, IIEF-5: international index of erectile function-5, ONTARGET: ongoing telmisartan alone and in combination with ramipril global endpoint trial, NR: not reported, TRANSCEND: telmisartan randomized assessment study in ACE iNtolerant subjects with cardiovascular disease, RCT: randomized controlled trial and SBP: systolic blood pressure

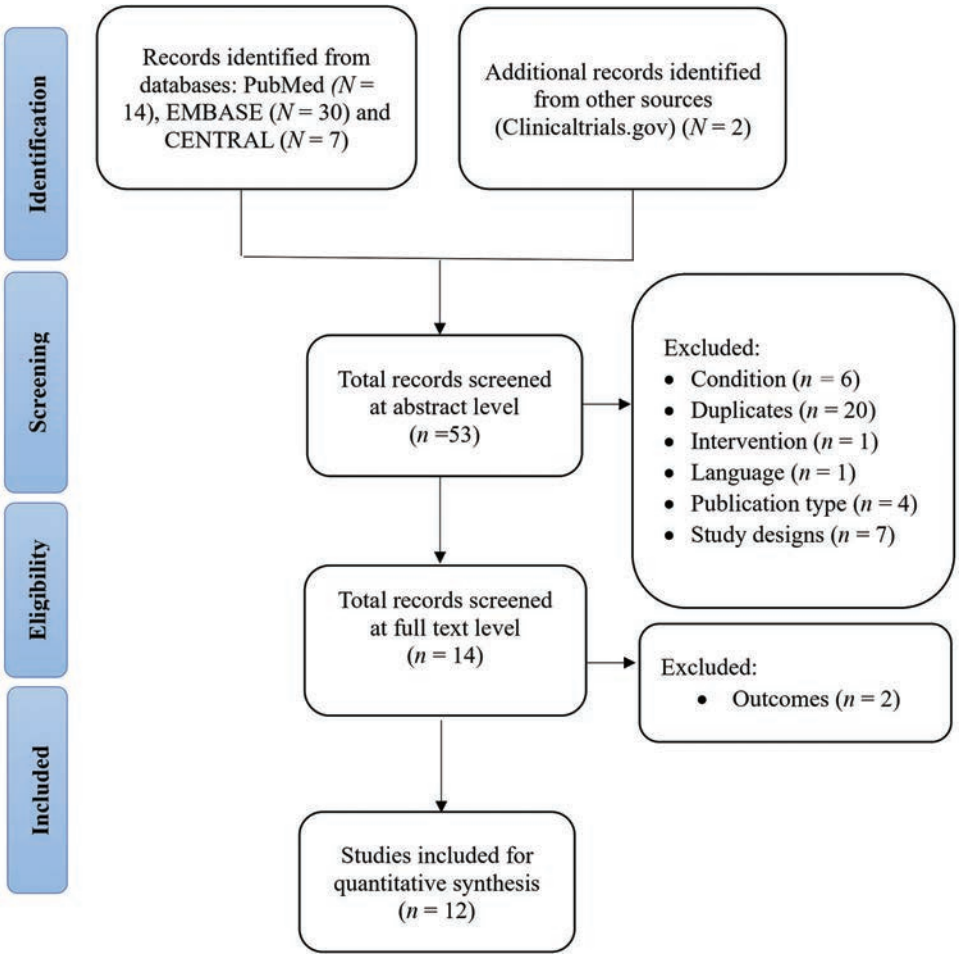

Figure 1: PRISMA flow chart of study selection and inclusion

combination compared to irbesartan monotherapy (25 ± 14 vs. 22 ± 15 mm Hg; $P < 0.001$).[24] Nearly 46% of patients with sexual dysfunction achieved a reduction in systolic blood pressure (≤140 mm Hg) on treatment with losartan.[18] Similarly, valsartan treatment for six months significantly reduced systolic blood pressure from 158 ± 16 to 136 ± 9 mm Hg ($P < 0.001$).[23] Both atenolol and valsartan therapy significantly reduced systolic blood pressure after 16 weeks of treatment (−21/9 vs. −23/9 mm Hg) when compared to placebo ($P < 0.01$).[21]

Similar rates of systolic blood pressure reduction were observed in patients on 16 weeks of treatment with valsartan monotherapy (−12%), valsartan + HCTZ combination (−11%), and conventional therapy (−11%).[22] The ONTARGET trial reported a greater reduction in systolic blood pressure with telmisartan + ramipril combination (−8.5 mm Hg) followed by telmisartan monotherapy (−7.6 mm Hg) and ramipril monotherapy (−5.4 mm Hg), respectively without any significant difference between the groups. Similarly, in the TRANSCEND substudy conducted in ACE intolerant patients, systolic blood pressure was reduced by 6.7 mm Hg in the telmisartan-treated group and only 1.2 mm Hg reduction in the placebo-treated group, respectively.[6]

Treatment with felodipine + irbesartan combination was effective in lowering overall blood pressure followed by felodipine + metoprolol, irbesartan + metoprolol, and irbesartan + HCTZ ($P < 0.01$).[26] A similar trend in systolic blood pressure reduction was observed in both felodipine + irbesartan groups.[25] Patients on treatment with candesartan + HCTZ showed a greater reduction in systolic blood pressure compared to those who received a placebo (mean change from baseline, 8.9 ± 15.7 mm Hg vs. 3.3 ± 15.9 mm Hg). Joseph *et al.* observed no correlation between blood pressure-lowering effect and improvement in erectile function ($P = 0.66$).[20] A detailed overview of the effect of ARBs on systolic blood pressure in patients with ED is reported in Table 3.

Effect of ARBs on change in diastolic blood pressure in patients with ED

Eight studies analyzed the changes in diastolic blood pressure among patients with hypertension and ED patients which displayed comparable results.[6,18,19,21-25]

Table 3: Comparative interpretation of outcomes in included studies

Study ID	Intervention	Reduction in SBP	Reduction in DBP	IIEF-5	Sexual activity	Changes in sex hormones
Llisterri, 2001[18]	Losartan	Baseline vs. 12 weeks treatment: 153 ± 13 vs. 139 ± 7 mm Hg; $P > 0.05$	Baseline vs. 12 weeks treatment: 89 ± 8 mm Hg vs. 83 ± 5 mm Hg; $P > 0.05$	NR	Improved sexual satisfaction (baseline vs. 12 weeks treatment): 7.3% vs. 58.5%; $P = 0.001$	NR
Fogari, 2002[21]	Atenolol and Valsartan	Baseline vs. 16 weeks treatment: −21/9 vs. −23/9 mm Hg; $P < 0.01$	Baseline vs. 16 weeks treatment: −16/4 vs. −14/4; $P < 0.01$	NR	Atenolol vs. placebo: reduced sexual activity (6.0–4.2 sexual intercourse episodes/month, $P < 0.01$) Valsartan vs. placebo: increased sexual activity (5.8–7.4 sexual intercourse episodes/month, $P = 0.058$)	Reduction of testosterone plasma levels with 16 weeks of atenolol treatment: 13.8 nmol/l, −24%, $P < 0.01$
Chiesa, 2003[22]	Valsartan vs. Valsartan + Hydrochlorothiazide vs. Conventional therapy	On 16 weeks treatment: −12% vs. −11% vs. −11%	On 16 weeks treatment: 11.6 ± 0.2 vs. 11.3 ± 0.5 vs. 9.9 ± 1.5 mm Hg	NR	Sexual activity: 61% vs. 40% vs. 35%	NR
Dusing, 2003[23]	Valsartan	Baseline vs. 6 months treatment: 158 ± 16 to 136 ± 9 mm Hg; $P < 0.001$	Baseline vs. 6 months treatment: 94 ± 9 to 82 ± 6 mm Hg	Baseline vs. 6 months treatment: Improved IIEF-5 scores 16.54 ± 8.27 vs. 23.14 ± 6.49 ($P < 0.0001$), sexual function and overall satisfaction	NR	NR
Baumhäkel, 2008[24]	Irbesartan + Hydrochlorothiazide vs. Irbesartan	−25 ± 14 vs. −22 ± 15 mm Hg; $P < 0.001$	No significant difference; $P = 0.08$	Baseline vs. 6 months treatment: Improved IIEF-5 scores (Irbesartan) 16.9 ± 9.2 vs. 20.6 ± 7.9; (Irbesartan + Hydrochlorothiazide) NR vs. 21.3 ± 7.1, Improved erectile function ($P < 0.0001$), orgasmic function ($P < 0.001$) and intercourse satisfaction ($P < 0.001$)	NR	NR
Bohm, 2010[6]	Telmisartan + Ramipril vs. Telmisartan vs. Ramipril ACE intolerant patients: Telmisartan vs. Placebo	−8.5 mm Hg vs. −7.6 mm Hg vs. −5.4 mm Hg 6.7 mm Hg vs. 1.2 mm Hg	NR NR	Baseline vs. 104 weeks treatment: IIEF-5 scores (Ramipril) 15.5 ± 6.2 vs. 14.5 ± 4.7, (Telmisartan) 15.8 ± 6.12 vs. 14.9 ± 4.9, (Telmisartan + Ramipril) 15.9 ± 6.3 vs. 14.8 ± 5.19 Improved erectile function NR	NR NR	NR NR
Yu, 2010[26]	Felodipine + Irbesartan, Elodipine + Metoprolol, Irbesartan + Metoprolol, and Irbesartan + Hydrochlorothiazide	No significant differences among groups ($P > 0.05$)	NR	Improved sexual desire	NR	No significant differences in testosterone and sex hormone-binding globulin levels
Segal, 2011[27]	Irbesartan vs. Non-irbesartan group	NR	NR	Baseline vs. 24 weeks treatment: Elevated IIEF-5 scores (Irbesartan) 23.4 ± 0.5 vs. 22 ± 0.7, (Non-irbesartan group) 14.1 ± 3.1 vs. 15.2 ± 2.0	NR	NR
Chen, 2012[19]	Tadalafil, Losartan, Losartan + Tadalafil	NR NR NR	NR NR NR	Baseline vs. 12 weeks treatment: Improved IIEF-5 scores 9.4 ± 3.7 vs. 16.0 ± 4.6; $P < 0.05$ 9.7 ± 3.5 vs. 13.3 ± 5.0; $P < 0.05$ 10.0 ± 4.0 vs. 18.6 ± 4.8; $P < 0.05$	NR NR NR	NR NR NR

Table 3: Continued

Study ID	Intervention	Reduction in SBP	Reduction in DBP	IIEF-5	Sexual activity	Changes in sex hormones
Yang, 2013[25]	Felodipine + Irbesartan and Felodipine + Metoprolol	Decreased progressively by fourth week and remained stable through 48th week in both the groups	Decreased progressively by fourth week and remained stable through 48th week in both the groups	Baseline vs. 48 weeks treatment: Improved IIEF-5 scores (Felodipine + Irbesartan) 20.5 ± 6.7 vs. 20.8 ± 6.4, (Felodipine + Metoprolol) 20.5 ± 6.5 vs. 20.5 ± 6.6 Improved sexual desire with felodipine + irbesartan combination ($P = 0.022$)	NR	Reduction in 8-hydroxy-2′-deoxyguanosine and malondialdehyde ($P < 0.001$); no significant differences in testosterone and sex hormone-binding globulin levels
Joseph, 2018[20]	Candesartan + Hydrochlorothiazide vs. Placebo Rosuvastatin vs. Placebo	8.9 ± 15.7 mm Hg vs. 3.3 ± 15.9 mm Hg NR	NR NR	Baseline vs. 302 weeks treatment: Improved IIEF-5 scores (Candesartan + Hydrochlorothiazide) 23.0 ± 5.5 vs. 21.8 ± 5.8, (Placebo) 23.0 ± 5.7 vs. 22.1 ± 5.7, (Rosuvastatin) 22.9 ± 5.7 vs. 22.0 ± 5.7, (Placebo) 23.1 ± 5.6 vs. 21.9 ± 5.8	Improvement in erectile function ($P = 0.66$) NR	NR NR
Correia, 2022[28]	Alpha blockers, angiotensin-converting enzyme inhibitors, calcium channel blocker, β-blockers	NR	NR	Prevalence of ED in men (%): mild (70.1%), moderate (21.9%), severe (9.1%)	NR	NR

ACE: angiotensin-converting enzyme, CV: cardiovascular, DBP: diastolic blood pressure, ED: erectile dysfunction, HR: Hazard ratio, IIEF-5: international index of erectile function-5, NR: not reported, P: probability, SBP: systolic blood pressure, vs.: versus, %: percentage. SBP and DBP data are mean ± SD mm Hg

Similar levels of decrease in diastolic blood pressure were observed with irbesartan monotherapy and irbesartan + HCTZ combination therapy (−22 ± 15 vs. −25 ± 14 mm Hg).[24] Similarly, valsartan and atenolol treatment for 16 weeks resulted in a significant decrease in diastolic blood pressure (−16/4 vs. −14/4; $P < 0.01$). Normalization of blood pressure (diastolic blood pressure <90 mm Hg) was achieved among patients with or without sexual dysfunction (85% and 94%, respectively), receiving both valsartan (49%) and atenolol (44%).[18,21]

Treatment with valsartan for six months reduced diastolic blood pressure from 94 ± 9 mm Hg to 82 ± 6 mm Hg.[23] Patients on valsartan monotherapy and valsartan + HCTZ combination therapy showed a greater decrease in diastolic blood pressure compared to conventional therapy (11.6 ± 0.2, 11.3 ± 0.5, and 9.9 ± 1.5 mm Hg), respectively.[22] Likewise, a similar trend in diastolic blood pressure decline was observed in patients receiving felodipine + irbesartan and felodipine + metoprolol combinations [Table 3].[25]

Effect of ARBs on erectile function analyzed by IIEF-5 score

Nine studies[6,19,20,23-28] examined IIEF-5 scores in patients with hypertension and ED who received ARBs. Patients treated with irbesartan for 12 months reported elevated IIEF-5 scores compared to those in non-irbesartan group (14 ± 2.6 vs. 7.2 ± 1.6, $P < 0.05$).[27] Similarly, treatment with irbesartan monotherapy and irbesartan + HCTZ combination therapy significantly ($P < 0.0001$) improved erectile function, orgasmic function, and intercourse satisfaction irrespective of the dosages. An improvement in erectile function is believed to be partially dependent on the reduction of arterial pressure and its effect on endothelial function.[24]

Valsartan treatment for six months significantly ($P < 0.0001$) improved all five domains of IIEF, namely, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction in patients with hypertension.[23] The IIEF-5 scoring showed substantial difficulty in maintaining an erection to completion of intercourse and profound unsatisfactory coitus post-antihypertensive medication. Prevalence for ED was distributed as mild (12–21 IIEF-5 score) accounted for 255 (70.1%), moderate (8–11 score) accounted for 76 (21.9%), and severe (5–7 score) accounted for 33 (9.1%).[28]

A greater improvement in erectile function was observed in patients treated with telmisartan, ramipril, and in combination (telmisartan + ramipril).[6] Similarly, an improved sexual function was observed among all

treatment groups where the felodipine + irbesartan combination showed the least effect ($P < 0.05$) compared to felodipine + metoprolol, irbesartan + metoprolol, and irbesartan + hydrochlorothiazide. However, the study suggested felodipine + irbesartan combination as a better treatment choice to prevent ED and improve adherence.[26] A significant ($P < 0.05$) improvement in the mean IIEF-5 scores was observed with tadalafil (9.40 ± 3.66 vs. 16.00 ± 4.55), losartan (9.68 ± 3.46 vs. 13.28 ± 4.92), and losartan + tadalafil combination (9.94 ± 4.02 vs. 18.61 ± 4.83) compared to baseline scores. Additionally, losartan + tadalafil combination therapy in diabetic patients proved to be effective on erectile function.[19]

A significant improvement in sexual desire was observed in patients on felodipine + irbesartan combination therapy compared to the felodipine + metoprolol-treated group ($P = 0.022$).[26] However, IIEF-5 did not differ significantly from the baseline score in both treatment groups.[25] In the HOPE-3 trial, the mean IIEF-5 score did not differ between the candesartan + HCTZ combination and placebo group (1.6 ± 0.3 vs. 1.6 ± 1.3, $P = 0.10$) posttreatment [Table 3].[20]

Irrespective of the dosage and addition of other antihypertensives, irbesartan treatment for six months significantly improved erectile function ($P < 0.0001$), orgasmic function ($P < 0.001$), and intercourse satisfaction ($P < 0.001$).[24] In Dusing *et al.* study, an improvement in sexual function and overall satisfaction was observed.[23] The data suggests that there is no correlation between sexual dysfunction and arterial pressure.

Effect of ARBs on sexual activity assessed by self-administered questionnaire

A validated self-administered questionnaire[18] ("symptom-finding" questionnaire) assessed sexual activity and sexual satisfaction with losartan treatment in patients with hypertension. However, in all other included studies,[6,19,20,23-28] the IIEF questionnaire was used to assess erectile function in patients with hypertension. A significant improvement ($P < 0.001$) in erectile function along with satisfaction and frequency of sexual activity from 7.3% at baseline to 58.1% was observed in patients treated with losartan for 12 weeks. The study suggests ARBs as an alternative and a better choice to improve the quality of life of hypertension patients with and without ED.[18]

Effect of ARBs on sexual hormonal changes in patients with ED

Three studies[21,25,26] compared various antihypertensive interventions that induced sexual hormonal changes in patients with hypertension and ED.

Patients treated with felodipine + irbesartan combination for 48 weeks showed a significant reduction ($P < 0.001$) in 8-hydroxy-2′-deoxyguanosine and malondialdehyde levels that reduced oxidative stress. However, no significant difference was observed between the felodipine + irbesartan, and felodipine + metoprolol-treated groups ($P > 0.05$) in terms of testosterone and sex hormone-binding globulin levels. An improvement in sexual desire values was observed in patients treated with the felodipine + irbesartan combination ($P = 0.022$).[25] Patients treated with felodipine + irbesartan, felodipine + metoprolol, irbesartan + metoprolol, and irbesartan + HCTZ combination therapies showed a change in the testosterone and sex hormone-binding globulin levels with no significant differences between the treatment groups ($P > 0.05$).[26] A significant reduction of testosterone plasma levels was observed with 16 weeks of atenolol treatment (13.8 nmol/l, −24%, $P < 0.01$).[21]

Effect of ARBs on sexual activity (sexual intercourse episodes/weeks) in patients with ED

Of the 12 included studies, only one study[22] investigated sexual intercourse episodes per week. The study reported a remarkable increase in sexual activity with valsartan monotherapy (61%) followed by valsartan + HCTZ combination therapy (40%), while it reduced by 35% in the control group.

CV events and CV events induced deaths in patients with ED

Of the 12 included studies, the ONTARGET and TRANSCEND substudy conducted by Bohm *et al.*[6] was the only study that investigated the association between ED and CV events. The study reported that ED was predictive of all-cause mortality (HR: 1.84, 95% CI: 1.21–2.81, $P = 0.005$) and the composite primary outcomes (HR: 1.42, 95% CI: 1.04–1.94, $P = 0.029$) consisting of CV death (HR: 1.93, 95% CI: 1.13–3.29, $P = 0.016$), myocardial infarction (HR: 2.02, 95% CI: 1.13–3.58, $P = 0.017$), hospitalization for heart failure (HR: 1.2, 95% CI: 0.64–2.26, $P = 0.563$), and stroke (HR: 1.1, 95% CI: 0.64–1.9, $P = 0.742$).[6]

DISCUSSION

ED is a common complaint in men with hypertension and is closely correlated with multiple overlapping risk factors.[29,30] Management of ED in patients with hypertension remains challenging as the treatment of hypertension may adversely affect sexual function.[31] This may also impair the quality of life and medication adherence, particularly in patients with highly prevalent diseases like hypertension.[18] This systematic review analyzed the efficacy of ARBs in

hypertension and ED outcomes compared to other classes of antihypertensive drugs. Arterial hypertension is a well-known risk factor contributing to high CV morbidity and mortality.[23] Elevated blood pressure is significantly associated with decreased sexual activity in patients with hypertension.[32] According to Kifor *et al.*[10] diastolic blood pressure has a U-shaped correlation with ED prevalence, indicating that both low and high diastolic blood pressure increases the prevalence of ED. An improvement in arterial blood pressure was one of the outcomes that analyzed the efficacy of interventions. A significant reduction in systolic and diastolic blood pressure was observed with ARB monotherapy as well as combination therapy among patients with hypertension in the included studies. Reduction in these risk factors was associated with an improvement in erectile function, which in turn resulted in a highly significant improvement in orgasmic function, frequency of sexual activity, and overall satisfaction in patients.[18,19,22,23,26] Findings of ONTARGET, TRANSCEND, and HOPE trials revealed that ARBs achieved blood pressure reduction but without any significant difference between the treatment groups, in contrast to other included studies.[6,20]

ARBs act by reducing arterial pressure by blocking the action of angiotensin II and thus preventing its binding to the angiotensin II receptor. However, the mechanism by which it improves erectile function is not clear. Inhibition of angiotensin II, the main effector of the renin-angiotensin system, may help improve erectile function since angiotensin II levels are higher in the cavernous blood than in the systemic blood.[33] Thus, the positive effects of ARBs in improving erectile function are likely to be dependent on the reduction in arterial pressure. An improvement in endothelial function following a reduction in arterial pressure was evident in a study conducted on patients with metabolic syndrome which was marked by improved sexual function.[24] Similarly, clinical evidence shows the beneficial role of ARB therapy in diabetic and non-diabetic ED.[19,24] However, combination therapy with a phosphodiesterase 5 inhibitor, a first-line drug for improving erectile function, would be a better choice for diabetic ED due to the complex pathogenesis.[19] ED is the main reason for impaired sexual activity that increases with the advancement of age. The role of angiotensin II in the pathogenesis of ED causes the contraction of cavernosal smooth muscle and the termination of spontaneous erection. The incidence of ED is largely dependent on drug treatment in patients.[22] According to Saleem *et al.*[11] ED is more common in treated men with hypertension than untreated men. Certain antihypertensive drugs, most notably diuretics and β-blockers have been linked with a deterioration in sexual function.

Sexual function was the second outcome to measure the efficacy of ARBs analyzed by calculating the IIEF-5 score. It is a widely used, multidimensional self-report questionnaire to assess male sexual function. It has been preferred as a primary endpoint in clinical trials of ED and for determining the severity of ED. IIEF-5 questionnaire has five subdomains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.[34] An improvement in erectile function was observed with an increased IIEF-5 score which indicates improved domains of sexual function in almost all studies.[6,18-20,25,26] ARB-induced selective blockade of angiotensin receptor reduces hypertension and vascular inflammation, which subsequently improves the endothelial function and erectile function.[23,24,27] However, a study conducted in patients with ED postradical prostatectomy suggests that improvement in erectile function is independent of blood pressure.[27] Similarly, improvement in sexual function in the losartan group was independent of blood pressure reduction whereas the control group showed comparable results in blood pressure reduction. This effect may be due to the regulation of penile blood vessels or neuronal signals from the sacral spine.[18]

Furthermore, in ONTARGET, TRANSCEND substudy, ARBs did not show any significant difference in IIEF score from the baseline.[6] These findings were consistent with the observation of a randomized controlled trial (HOPE-3 trial) where long-term therapy of ARB combination therapy did not improve the IIEF score.[20] In these trials, ARBs showed a neutral effect on ED, which means they neither improved nor adversely affected ED. In addition, screening for ED in male patients with hypertension using the IIEF-5 questionnaire, if done routinely, may lead to earlier diagnosis, medication adjustments, and advice on lifestyle changes, including cigarette smoking cessation. However, the need for discontinuing ARB therapy does not arise and can be considered for long-term management of indications.

The treatment of ED in hypertensive patients may require a combination of drugs, depending on the effects of each drug on the erectile function. Some antihypertensive drugs, such as beta-blockers,[35] thiazide diuretics,[36] and calcium channel blockers, may increase the risk of ED, while others, such as nebivolol,[37] ACEIs, and ARBs,[23] may have a protective effect. Therefore, combination therapies should be carefully selected for hypertensive patients with ED, considering the possible facilitatory or contradictory effects of the second or third drug.

One of the major factors influencing medication adherence is the side effects associated with antihypertensive

therapy.[18,19] Studies have shown that ARBs enhance sexual performance, unlike other classes of antihypertensives such as diuretics, β-blockers, and calcium channel blockers which are known to have negative effects.[12-15,22] A significant increase in sexual activity was found in ARB treated group in a study conducted on men with hypertension. ARBs show an age-dependent pattern in sexual activity where a younger group of patients showed higher activity than elderly patients.[22] An enhancement in sexual activity is associated with an enhancement in medication adherence and quality of life of patients among all age groups. Another study suggests that β-blocker atenolol and the angiotensin II receptor antagonist valsartan have different effects on sexual activity and plasma testosterone levels, and valsartan may offer some advantages in terms of sexual life quality despite similar hypotensive action.

ED can not only affect the individual and his partner but also his community. It can reduce the productivity and performance of men at work due to stress, anxiety, depression, and low self-esteem,[38] as well as their participation in social activities. ED can also increase the health care costs and burden on the health system, as more men may seek medical help or use alternative treatments. Since the incidence of ED is higher in patients with hypertension, an appropriate treatment regimen for hypertension that is, also effective for ED will benefit the community by enhancing social and economic development and reducing the healthcare burden.

According to prior published studies, testosterone can regulate the frequency of erectile function and sexual desire in men with hypertension. Sex hormone-binding globulin is primarily involved in the transportation as well as regulation of sexual hormones in the blood in addition to testicular spermatogenic activity.[27] Previous studies have reported the negative effect of β-blockers on androgen level, which impacts male sexual function. However, ARBs did not affect the levels of testosterone and sex hormone-binding globulin in the included studies.[25,26] Hence, ARBs would be an alternative therapy for hypertension patients with lower androgen levels. The pathophysiology of both hypertension and ED involves oxidative stress and inactivation of nitric oxide which plays a major role in erectile function.[25] 8-hydroxy-2′-deoxyguanosine and malondialdehyde levels are considered oxidative stress indicators.[39,40] Angiotensin II-induced activation of oxidative stress can be inhibited by blocking the action of angiotensin II receptors, which in turn improves nitric oxide concentration.[25] The decreased concentration of oxidative stress markers and increased sexual desire of patients elucidated the beneficial role of ARBs in depressing the process of oxidative stress in the included studies.[25,26] Finally, the study found that prior ED is a strong predictor of all-cause mortality and CV events. Patients with severe ED are at a higher risk than patients with no or mild ED. The progression of the ED influences all-cause death and composite CV events.[6]

ED is a complex condition that can have various causes, such as vascular, neurological, psychological, and hormonal factors. There is no single treatment that works for everyone with ED, and different patients may respond differently to different treatments. Usually, the first line of treatment for ED is lifestyle modification and oral medication. However, some cases are more complicated and require more invasive treatment methods, such as intracarvenosal injections or surgical implants or devices.[41] Therefore, it is important to diagnose the actual cause of ED by using proper screening techniques, taking a complete medical and surgical history, and performing laboratory tests. This will help in selecting the best treatment option for each patient. This study had several strengths. Previous systematic reviews and meta-analyses included only four randomized control trials with limited outcomes to evaluate the efficacy of ARBs. To our knowledge, this is the first systematic review conducted to analyze the efficacy of ARBs for ED in patients with hypertension. Additionally, the study includes observational studies, before and after studies with randomized control trials. The findings of this systematic review reinforce the effectiveness of ARBs in improving sexual function and quality of life in hypertension patients with ED.

This study also had several limitations. Firstly, the included studies were heterogeneous in their design, therefore, a meta-analysis was not feasible. The included studies vary in the study design, intervention, and outcome analyzed. All studies that met inclusion criteria and reported at least one of the pre-specified outcomes were included. Secondly, there was a limited number of studies available for review. Studies with less sample size were also included since they met the inclusion criteria.

CONCLUSION

ARBs significantly reduced arterial pressure and improved erectile function among participants in the intervention group. The results also show that ARBs depressed the process of oxidative stress and increased sexual desire among the participants. Its neutral effect on levels of serum testosterone and sex hormone-binding globulin makes it an ideal choice for hypertension patients with lower androgen levels. Based on the above-outlined studies, ARBs are effective for treating ED in men with hypertension. Both

monotherapy and combination therapies are beneficial for improving erectile function and compliance among patients.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

A brief review of the neuroimaging modalities in schizophrenia and their scope

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Abstract

Schizophrenia is a serious mental disorder characterized by diverse symptoms, including hallucinations, delusions, and disorders in thinking, behavior and cognition. Its etiology is multifactorial involving genetic, environmental, developmental, and neurobiological factors. Neuroimaging studies have significantly contributed to understanding the underlying neural abnormalities associated with this disorder. Reduced brain volume was observed in frontal and temporal lobes in most studies using structural imaging techniques. Hypofrontality was observed in functional studies. Neuroimaging also aids in differentiating structural lesions causing symptoms mimicking schizophrenia. However, challenges persist due to variables such as age, gender, comorbidities, therapy history, substance use, and coexisting psychiatric conditions, which are often insufficiently controlled for, in the literature. This review article comprehensively consolidates the diagnostic and prognostic potential of various neuroimaging techniques in schizophrenia.

Keywords: Functional, hypofrontality, magnetic resonance imaging, neuroimaging, positron emission tomography, schizophrenia, structural

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INTRODUCTION

Schizophrenia is a complex and chronic mental disorder that severely affects the thought, perception, affect, and cognition of an individual. The etiology is diverse with a multitude of factors including genetic, environmental, developmental, and neurobiological. Neuroimaging studies facilitate the understanding of the cerebral correlates of the various symptoms of schizophrenia. From the majority of the neuroimaging studies based on chronic patients with schizophrenia, it is difficult to conclude whether the observed brain changes had preceded the disease or developed during the illness. Furthermore, antipsychotic treatment can also affect the brain architecture. Studies on drug naïve patients of schizophrenia, high-risk groups, and family studies may help to understand the pathogenesis. Disruption of communication between different cerebral regions may account for the central pathology of schizophrenia. [1-4] This article aimed to equip clinicians with knowledge of various neuroimaging techniques used in schizophrenia, with a focus on their current and potential future clinical applications.

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SEARCH STRATEGY

A systematic and detailed search strategy was employed to mark the relevant articles in various scientific databases like PubMed, Web of Science, and Scopus. The keywords for the search included a broad range of MeSH keywords related to schizophrenia and neuroimaging techniques, whereby 8640 studies were found. After excluding studies published before 2010 the number came down to 6245. Further, after the exclusion of non-human studies, clinical trials, preprints, letters to editors, perspectives, thesis, and non-English language articles, 1129 articles were considered. The name of the corresponding author, design of the study, method of recruitment, demographics, clinical parameters, and imaging methodology were used to detect redundancies. Finally, title and abstract screening was done for 348 articles, followed by the full-text screening and detailed study of 102 articles.

STRUCTURAL NEUROIMAGING MODALITIES

Computed tomography

In patients presenting with acute psychotic symptoms that pose a diagnostic dilemma regarding organicity, an initial evaluation by computed tomography (CT) scan of the brain can rule out stroke, tumor, trauma, hemorrhage, and other organic lesions. CT scan does not present any signature findings of schizophrenia. Research suggests that the volume reduction found in the brain of patients suffering from schizophrenia may result from the long-term use of psychotropic medications, and is also associated with the total antipsychotic dosage. When compared to patients receiving atypical antipsychotics, patients receiving conventional antipsychotics showed a greater reduction of brain volume.[5] Higher prevalence of aberrant features like cortical atrophy, ventriculomegaly, and cavum septum pellucidum has been found in schizophrenia as compared to general populations.[6-8]

Standard magnetic resonance imaging

The gold standard for assessing schizophrenia in both clinical and research settings is magnetic resonance imaging (MRI) and functional imaging. The prefrontal cortex, superior, middle, and inferior temporal gyri, superior, middle, and inferior frontal gyri, hippocampus, parahippocampal gyrus, insular cortex, caudate nuclei, thalami, and supramarginal and angular gyri have all shown reduction of grey and white matter in MRI studies on patients with schizophrenia. Histological evidence supports these data by showing a decrease in dendritic and synaptic density, which may indicate abnormalities in brain transmission (the disconnection hypothesis).[9-13]

FUNCTIONAL NEUROIMAGING MODALITIES

Resting-state functional magnetic resonance imaging

Resting-state functional MRI (RS fMRI) measures brain activity during periods of rest, without the subjects performing any specific task. RS fMRI captures the low-frequency fluctuations in the signal which is dependent on the blood oxygen level (BOLD signal). The default mode network (DMN) of the brain becomes more active while the brain is at rest and turns less active during cognitive tasks. Studies have consistently reported default mode functional hyperconnectivity in schizophrenia. Another common finding in schizophrenia is the disturbance in anti-correlation between the DMN and task-positive networks (TPNs), suggesting altered functional interactions between different brain networks.[14,15]

Studies have highlighted functional abnormalities in multiple cerebellar regions in schizophrenia.[16] Abnormalities were observed in prefrontal regions, especially with regard to that in the orbitofrontal and dorsolateral prefrontal areas, as well as the left superior temporal gyrus overlap in both task-related and resting state fMRI studies in schizophrenia patients. Disruption in global topology measures has been observed both in patients with schizophrenia and in healthy relatives of schizophrenia patients but to a diminished level in the latter, suggesting potential endophenotypes.[15]

Dynamic functional network connectivity (DFNC) is an analytic approach that assesses the temporal coordination of cerebral networks with respect to a time scale. Studies using DFNC in schizophrenia and bipolar disorder showed that patients differed from healthy controls in dynamic brain network patterns. Such abnormalities in schizophrenia tend to return to normal after treatment with antipsychotic medications. Another technique, amplitude of low-frequency fluctuations (ALFF), quantifies intrinsic low-frequency oscillations in the resting brain. Abnormal regional homogeneity patterns have been reported in schizophrenia, bipolar disorder, and high-risk individuals predisposed to develop schizophrenia in later life. Drug-naïve individuals with a young age of onset of schizophrenia displayed an increase in regional homogeneity in the medial prefrontal, inferior parietal, and superior temporal brain areas.[17,18]

Task-related functional magnetic resonance imaging

Research using task-based approaches in the context of schizophrenia has revealed altered activation patterns within certain regions of the brain such as the prefrontal cortex, temporal lobes and hippocampus. A recent synthesis of multiple studies discovered diminished activation in specific areas like the dorsomedial prefrontal cortex, right inferior

frontal gyrus, and supplementary motor area when attention and vigilance tasks were impaired. Similarly, when engaging in tasks involving social interaction, decreased patterns of activation were noted in the right angular gyrus. A study investigating auditory hallucinations found activation primarily situated in the left insula and inferior parietal lobule, both linked to reduced grey matter volume. In the context of the Stroop task, individuals with schizophrenia demonstrated dysfunction in the DMN. Exposure to negative threat words prompted hyperactivation in certain brain regions in schizophrenia patients compared to control groups. Within Cognitive-based paradigms, individuals with schizophrenia typically exhibit poorer task performance and distinct activation patterns in relevant brain circuits when compared to their healthy counterparts.[19-22]

Arterial spin-labelled magnetic resonance imaging

Arterial spin-labeled (ASL) MRI directly assesses cerebral blood flow by utilizing naturally present arterial blood water as a diffusible tracer. Research has yielded varying results due to the relatively limited participant numbers and differences in methodologies. However, consistent findings have indicated reduced blood flow in the frontal region during rest. One study identified heightened flow of blood in the thalamus among individuals not receiving medication, while another investigation noted increased blood flow in the putamen and inferior temporal gyrus, alongside reduced flow in frontal and occipital regions. Investigations have linked cognitive impairments in schizophrenia to diminished white matter integrity, which can be associated with variations in blood perfusion between white and grey matter. This association was also noticed in the corpus callosum of patients in the initial stages of schizophrenia, regardless of illness duration and medication dosage. [23,24]

Positron emission tomography

Positron emission tomography (PET) imaging stands as a potent technique for investigating molecular and cellular-level biological processes through the utilization of imaging agents tagged with positron-emitting radionuclides. The integration of PET and MRI in simultaneous PET/MR brain imaging capitalizes on PET's molecular sensitivity and specificity alongside MRI's high-resolution anatomical details and fMRI brain activity measurements.[25,26]

Positron emission tomography using fluorodeoxyglucose (FDG-PET)

Research using positron emission tomography using fluorodeoxyglucose (FDG-PET) has highlighted a phenomenon termed "hypofrontality" in schizophrenia, characterized by a reduced frontal-to-occipital lobe metabolic ratio in the utilization of FDG. Patients with schizophrenia display diminished metabolic rates in the frontal and temporal cortex. Certain theories link schizophrenia-related hypometabolism to synaptic dysfunction. Differential FDG PET results have been noted among various clinical presentations of schizophrenia. The negative/deficit symptom subtype is associated with lower glucose absorption in certain brain regions compared to the positive symptom subtype. PET studies in schizophrenia have predominantly concentrated on the dopamine system, which has confirmed the mechanism of action for antipsychotic medications. Understanding the therapeutic window of D2 receptor blockade has led to adjusted antipsychotic dosing recommendations. PET investigations have also suggested potential changes in brain glial cell quantity or function.[25-28]

Positron emission tomography studies with non-fluorodeoxyglucose tracers

PET tracers binding with Synaptic Vesicle Protein 2A (SV2A) have emerged to explore synaptic terminal markers in schizophrenia. Studies have indicated reduced uptake of tracers in the frontal and anterior cingulate cortices, as well as the hippocampus and temporal regions, among chronic patients with schizophrenia. Lower levels of SV2A have been correlated with reduced synaptic density in post-mortem analyses. Antipsychotic treatment appears to have a negligible impact on such reduction in synaptic density.[29,30]

PET agents binding to cannabinoid receptors have been explored in schizophrenia due to the connection between cannabis and acute psychoses. A study observed heightened cannabinoid receptor availability in specific brain regions including the nucleus accumbens, which was linked to reduced negative symptoms. Another study involving non-smokers with recent-onset psychosis identified decreased availability of alpha 7 nicotinic acetylcholine receptor (α7-nAChR) in the hippocampus and cingulate, which correlated with cognitive deficits. Lower uptake of tracers in the hippocampus of patients with schizophrenia correlated with reduced cognitive performance. [31-33]

Diffusion tensor imaging

Diffusion tensor imaging (DTI) has revolutionized the exploration of white matter tracts in the brain. A comprehensive study conducted by the ENIGMA group unveiled the occurrence of colossal microstructural white matter irregularities in schizophrenia.[34] Investigations concerning white matter tracts associated with the amygdala, a pivotal brain structure influencing behavior and emotion, specifically the uncinate fasciculus connecting the amygdala to the regions concerning executive functions like the medial and orbitofrontal cortices, have demonstrated reduction in fractional anisotropy among patients with

schizophrenia. Consistent reductions in fractional anisotropy are evident throughout the corpus callosum in patients with schizophrenia, as well as in individuals at risk of developing schizophrenia.[35,36]

DTI findings have also exhibited potential links to treatment responsiveness in schizophrenia patients. A negative correlation has been found between dopamine synthesis and connectivity of the dorsolateral prefrontal cortex with the associative striatum, in cases responding to treatment, unlike treatment-resistant individuals. More pronounced disruption of the frontostriatal network has been reported from the former group. The implications of reduced fractional anisotropy in schizophrenia are multifaceted, manifesting as positive and negative symptoms, executive dysfunction, cognitive decline and social dysfunction. Studies centered on first-episode psychosis have evidenced reductions in whole-brain fractional anisotropy, particularly in projection, commissural, and association fibers. Investigations within first-episode psychosis patients have spotlighted abnormal DTI and resting-state fMRI findings in the thalamus, coinciding with volumetric and fMRI research supporting the thalamocortical connectivity dysfunction hypothesis. [37,38]

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) represents a non-invasive imaging method quantifying neurometabolites linked to brain-related neurological and metabolic processes. MRS studies reveal compromised neuronal integrity and function in schizophrenia. N-acetyl aspartate (NAA), a marker of neuronal health, exhibits reductions in schizophrenia, likely reflecting neuronal disruption. MRS findings consistently suggest elevated levels of glutamate neurotransmitter-related metabolites, consistent with the hypothesis of NMDA receptor dysfunction. Studies exploring the effects of antipsychotic drugs in schizophrenia consistently report reduced glutamatergic metabolites. Lactate levels in schizophrenia indicate potential mitochondrial dysfunction and a shift towards "anaerobic glycolysis." Phosphorus MRS studies in schizophrenia yield varying outcomes for phosphodiesters, phosphomonoesters, and inconsistent patterns in ATP and phosphocreatine concentrations. Research demonstrates a significantly reduced NAD+/NADH ratio in schizophrenia, implying reductive stress and impaired mitochondrial metabolism.[39-41]

Magnetoencephalography

Magnetoencephalography (MEG) serves as a neuroimaging tool measuring magnetic fields generated by brain intracellular electric currents. MEG experiments can be event-related or block designs, correlating neurophysiological events with external stimuli or comparing sustained cognitive/emotional states. Resting-state activity findings in schizophrenia yield contradictory results across frequency bands, necessitating larger samples and standardized analysis protocols for more dependable conclusions. MEG studies consistently show aberrant event-related fields (ERFs) during cognitive tasks and sensory processing activities, with impaired high gamma-band (>60 Hz) oscillations in schizophrenia. [42-45]

The Indian research scenario

In India, the study of schizophrenia has evolved significantly with Indian researchers providing valuable insights regarding the epidemiology, disease trajectory and the phenomenology of schizophrenia.[46] Neuroimaging studies performed in India have shown reduction in cortical volume in areas like the hippocampus, amygdala, superior temporal gyrus and anterior cingulate cortex in individuals suffering from schizophrenia. Also, it has been observed that there was a greater volume reduction in the superior temporal gyri in patients with predominantly negative symptoms of schizophrenia, than those with predominantly positive symptoms.[13] Abnormalities in cavum septum pellucidum has been reported in a substantial number of patients with schizophrenia, pointing towards the neurodevelopmental hypothesis of schizophrenia.[47] A DTI based study conducted on Indian subjects failed to find significant difference in fractional anisotropy measures between treatment responsive and treatment resistant cases of schizophrenia.[48] Another DTI based study has shown reduced fractional anisotropy in the cingulate gyrus in patients with schizophrenia who have auditory hallucinations.[49] A study using fMRI has indicated that abnormalities occur in the frontal and limbic areas in high risk subjects who have a potential of developing schizophrenia in later life.[50]

FUTURE DIRECTIONS

Implementation of multimodal neuroimaging techniques could provide a holistic understanding of the composite pathophysiology of schizophrenia. Long-term studies tracking brain changes over time can reveal the dynamic trajectory of schizophrenia, pinpointing critical stages for intervention. Advanced machine learning algorithms can pick up intricate patterns within complex neuroimaging data, which can help predict the onset of schizophrenia and thus aid early intervention. The identification of imaging-based biomarkers could enable the adoption of customized treatment approaches to individual patients. Neuroimaging can also be utilized to assess the impact of novel pharmacological interventions for schizophrenia. Although neuroimaging research in schizophrenia has made significant strides recently, substantial work remains to be

done to comprehensively grasp the disorder and enhance treatment outcomes. [51-58]

CONCLUSION

Neuroimaging has substantially propelled our comprehension of the neurobiology of schizophrenia. Structural neuroimaging methods have unveiled widespread grey and white matter abnormalities, while functional neuroimaging techniques have pinpointed shifts in resting-state functional connectivity and task-related neural functioning. These neuroimaging discoveries have paved the way for the identification of potential neuroimaging-based markers for schizophrenia, thus aiding in early detection, diagnosis, and treatment planning, which in turn would improve the quality of life of individuals suffering from schizophrenia, and decrease the caregiver burden.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Changing Trends in the Management of Posttransplant Ureteric Stricture

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Abstract

Introduction: Chronic kidney disease (CKD) is a common disease now. Diabetes and hypertension are the main cause. Renal transplant is a gold standard treatment. Posttransplant stricture is also common, and changing trends in management are emerging.

Materials and Methods: It is a retrospective observational study in a tertiary care hospital in East India. The study duration was from January 2019 to December 2021. In total, 140 patients were studied, including both live and cadaveric transplants. A patient who developed posttransplant hydronephrosis or presented with acute kidney injury was evaluated with ultrasonography, intravenous urography, contrast-enhanced computerized tomography, and magnetic resonance imaging. Management was done with double J (DJ) stenting, percutaneous nephrostomy (PCN) insertion, or surgical intervention.

Results and Analysis: Twelve (8.6%) patients out of 140 developed posttransplant ureteric stricture. Five (41.7%) out of 12 patients were managed with long dura DJ stenting, and five (41.7%) were managed with PCN insertion and serial follow-up. Only two (16.7%) required ureteric reimplantation.

Discussion: Posttransplant ureteric stricture is a common complication following renal transplantation. Common causes are increased cold ischemia time, ureteral edema, clots, tumors, calculi, lymphocele, abscess, and hematoma. Other causes include kinking of the ureter and previously unrecognized pelviureteric junction obstruction. In the literature, the incidence of posttransplant ureteric stricture ranges from 2% to 10% in one study; and in another study, it is 1% to 9%. In our study, it is 8.6%.

Conclusion: Diagnosis of the posttransplant ureteric stricture should be prompt, and management should be given as early as possible for better graft survival.

Keywords: CKD, ESRD, postoperative ureteral stricture, posttransplant ureteric stricture, renal transplant

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INTRODUCTION

In the present era, chronic kidney disease (CKD) is a very common disease. The most common causes of CKD worldwide are hypertension, diabetes, IgA nephropathy, and congenital anomalies of the kidney and urinary tract. CKD is a burden on the workload for nephrologists, who often manage it medically. However, kidney transplantation is frequently recommended when medical care fails or the patient refuses to comply with it.[1]

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The first renal transplant was carried out in 1950. When comparing hemodialysis and peritoneal dialysis, it provides a longer survival benefit and a higher quality of life.

Renal transplant is more convenient than dialysis for the patients. It relieves the patient from the morbid complications of the dialysis. Preserving the renal graft function is essential for the kidney transplant's success as well as its after-care issues. Postoperative ureteral stricture is one of the many difficulties that persist despite significant advancements in surgical methods, immunosuppressive medication regimes, and supportive therapy. Risks to graft survival and frequent patient survival are associated with postoperative ureteral stricture. Risks to graft survival and frequent patient survival are associated with postoperative ureteral stricture.[2,3]

Rigid ureteral stricture after transplantation affects 1–9% of patients after surgery. It typically appears in the initial days or within the first year. It is the most frequent cause of ureteral blockage and is often observed three months following transplantation. This particular postoperative problem can be attributed to both internal and external sources.

Early ureteral obstruction can be due to technical faults during the construction of the ureteroneocystostomy, such as not using a ureteral stent, anastomotic edema, redundant ureteric length or extrinsic compression by lymphocele, hematoma, or abscess. Ureterovesical anastomotic strictures result from technical error or ureteral ischemia. Other causes for stricture development are related to urine leak, a component of graft rejection phenomena, or chronic infection. Also, BK and cytomegalovirus have been linked to ureteral stricture formation. Ureteral stricture development rates do not show a difference across the variety of types of urinary anastomosis.[3-5]

Balloon dilation or endoureterotomy may be considered for short, low-grade strictures, but open reconstruction is associated with higher success rates. Urine leak usually occurs in the early postoperative period. Nearly 60% of patients can be successfully managed with a pelvic drain and urinary decompression (nephrostomy tube, ureteral stent, and indwelling bladder catheter). Proximal, large-volume, or leaks that persist despite urinary diversion require open repair.

Prompt diagnosis and management are the cornerstones to preventing graft loss and, ultimately, patient survival. In this review, we try to uncover the various etiology and pathogenesis of the posttransplant stricture and paradigm shift of its management.[6]

MATERIALS AND METHODS

Our research, a retrospective observational study, was conducted in an Eastern Indian tertiary care hospital. The time frame for the study was from January 2019 to December 2021. Twelve of the 140 transplants completed during the study period had the characteristics of a ureteric stricture. Patients with CKD who sought treatment at the nephrology outdoor patient department made up the study population. Patients undergoing transplants, both living and cadaveric, were considered. The transplant was performed after the chosen patients were optimized. Every general and hemodynamic parameter was optimized in accordance with the specifications. There were more live-related transplants in our group. Every person who was chosen for the transplant is preoperatively assessed and scheduled for a renal transplant. They were asked to follow up in the nephrology outpatient department after surgery. Patients exhibiting signs and symptoms suggestive of ureteric stricture were screened throughout follow-up. The whole hemogram, serum urea and creatinine, and screening ultrasonography (USG) were used in the investigations to rule out hydroureteronephrosis. Depending on the serum creatinine level, those with hydroureteronephrosis in the screening USG were asked to have investigations such as IVP, contrast-enhanced CT (CECT), or magnetic resonance imaging (MRI) performed.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients presented with deteriorating renal function, such as increased serum urea creatinine levels. Some presented with features of acute kidney injury. Nonetheless, some presented with diminished urine output. Some often presented with features of fluid retention and congested cardiac failure due to volume overload. Pain was not a significant symptom as the patient with transplanted kidney and ureter were often denervated, and pain sensation was lost.

Imaging was used to make the diagnosis. USG screening was initially performed to check for hydroureteronephrosis. Based on the results of the USG, imaging such as CT, MRI, scintigraphy, and RGP was performed.

On the basis of the results, management was chosen. While some patients only needed PCN treatment, others needed double J (DJ) stents. Only a small percentage of patients needed ureteric reimplantation, a more intrusive treatment.

RESULTS AND ANALYSIS

In the study period, we had done 140 transplants, including both living and cadaveric transplant. Twelve patients who received this treatment experienced posttransplant ureteric stricture. Four (4) were females (33.33%), and 8 were males (66.67%). The age span was between 25 and 50 years. The age distribution suggests that the age group between 31 and 40 years is more prone to stricture (50%), followed by 41–50 (33.33%) and 21–30 (16.67%). Of these 12 patients, 8 (66.67%) reported within the first 3 months of the surgery, whereas 4 (33.33%) reported after 3 months. Presenting symptoms were overlapping, and many patients had presented with more than one symptom. Pain at the graft site was a common presenting feature (9/12; 75%), followed by decreased output and declining renal function (7/12; 58.3%), graft site edema (5/12; 41.7%), and, less frequently, signs of acute kidney injury and sepsis (4/12; 33.3%). Of the 12 patients, 11 had creatinine values higher than the baseline (1.5 mg/dL), accounting for 91.7% of the total. Eight patients (66.7%) had hemoglobin levels below 10 g/dL, and four patients (33.3%) had elevated total leucocyte counts. Urine cultures from five patients were positive, with *Escherichia coli* being the most common kind. USG screening was performed in 100% of patients. Ten patients (83.3%) had RGP performed; two of them also had nephrostograms to determine the precise site of the stricture [Figure 1]. Of the individuals who had DTPA (33.3%), three needed surgical intervention. Eight patients (67.7%) had CT scanning, seven underwent non-contrast CT scanning (NCCT), and just one patient underwent CECT (Cr-1.4). Considering the management of the patients, 10 patients (83.3%) were managed more conservatively. Five patients (41.7%) were managed with a long dura stent for 6 months [Figure 2]. Five patients (41.7%) managed with PCN insertion, and only two patients (16.7%) required ureteric reimplantation. Ten patients who were managed via a more conservative approach had shown complete response. One patient was kept on PCN, and another patient was put on a long dura stent. This was done to reduce the inflammation around the graft kidney site. Both patients who had not responded to the conservative management were treated surgically.

DISCUSSION

Today, CKD is one of the most common causes of morbidity and mortality worldwide. Diabetes and hypertension are the most common cause leading to CKD. All over the globe, scientists are trying immensely to sort out better management of CKD. Medical management is advancing very fast in the field of CKD management, but still, the gold standard treatment for these patients is renal transplant.

Renal transplantation has its own pros and cons. On the one hand, it improves the patient's quality of life, eliminates the need for dialysis, and prolongs life to a normal overall survival. On the other hand, it burdens the patient with lifelong immunosuppressive therapy leading to many

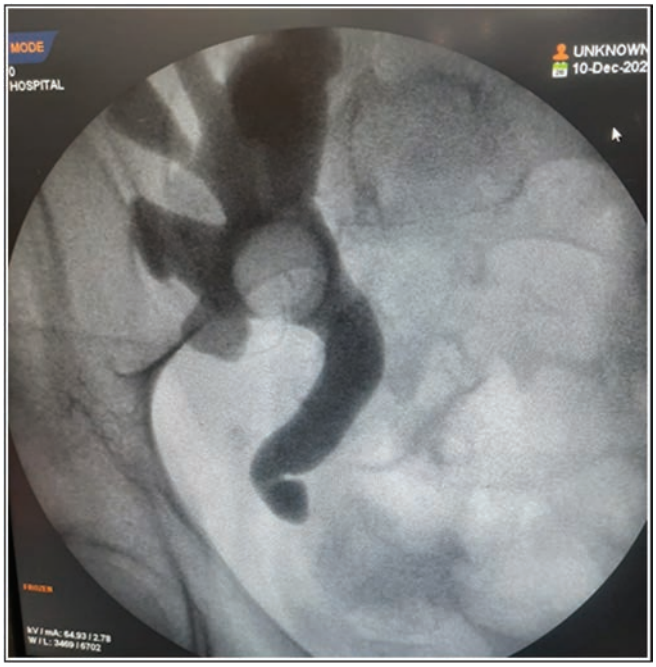

Figure 1: Nephrostogram of graft kidney and ureter

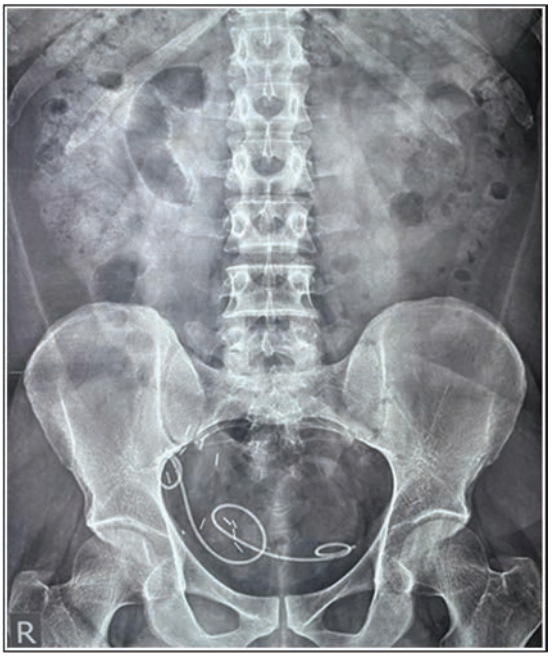

Figure 2: Placement of long dura stent

opportunistic infections. Even postoperative complications are also cumbersome. Posttransplant ureteric stricture is one postoperative complication in transplant patients. A review of the literature suggests that 1–9% of posttransplant patients develop postoperative ureteral stricture. In another study by Kumar *et al.*, they found a 2–10% stricture rate in posttransplant patients.[7,8] Our study also reveals similar results. In our study, we got stricture in 8.6% of cases.

The main causes and the risk factors for posttransplant ureteric stricture are various, which can be divided under various subheadings. Some risk factors are age more than 35 years, more than two transplant arteries, and increased cold ischemia time. Some intrinsic factors are ureteral edema, clots, tumors, and calculi. Extrinsic factors are lymphocele, abscess, and hematoma. Other causes include kinking of the ureter and previously unrecognized pelviureteric junction obstruction.[9]

Ureteric ischemia is now considered as the major cause of the ureteric stricture. The lower ureteric stricture accounts for 90% as it is the most distal part of the renal artery, hence it is more vulnerable to ischemia. The proximal part of the ureter is supplied by variable small arteries. So, it is always best to keep a DJ stent, as it is seen that in the absence of a DJ stent, there is a probability of early ureteric stricture due to ischemia.

Though the cause of early ureteric stricture is mainly due to ischemia, it can also be due to narrow and tightened neoureterocystomy. Some other causes are lymphocele, hematoma, and abscess. Faulty surgical technique is also a reason. Long donor ureter is also vulnerable to ischemia and may cause kinking, leading to intermittent obstruction.

The late cause of ureteric stricture is less well defined. It is probably due to the ischemic fibrosis. Immunosuppressive drugs such as corticosteroids and calcineurin inhibitors cause vasoconstriction, which may also lead to ischemia, followed by fibrosis. Ureterolithiasis and ureteric tumors are uncommon causes in posttransplant patients. In the literature, there was evidence of a three times increased risk in the incidence of bladder cancer in posttransplant patients due to the involvement of newly formed VUJ by a bladder tumor. It should be suspected in late presentation of ureteric stricture following transplant. Ureterolithiasis is relatively uncommon cause of posttransplant stricture, but data are sparse.

In our study, the patients treated with PCN insertion showed an 83.3% response rate. On follow up, they showed a complete cure. Various national and international studies have shown success rate of percutaneous nephrostomy (PCN) insertion is more than 98%. Tandem ureteral stent has been suggested to be more effective, but very limited data exists.[10] No patient in our study required DJ stent insertion following PCN, and only one patient required surgical intervention following PCN insertion.

A study by Lojanapiwat *et al.*[11] had shown that the success rate of ureteric stenting was between 62% and 86%. In our study, it is 83.3%. A review of the literature suggests that patients who presented within 3 months posttransplant had a better outcome than those presented later. It may be due to irreversible renal damage.

Surgical intervention is reserved for those who does not respond to either PCN or DJ stenting. The drawback of the surgical procedure is the chance of graft injury and graft failure. Various open and laparoscopic techniques can be used for surgical management. Procedures such as uretero-ureterostomy, uretero-neocystostomy, psoas hitch, Boari flap, transuretero-ureterostomy, intestinal substitution, and renal autotransplantation. All these above procedures have their own advantages and disadvantages. In our study, we did two open procedures, both of them ureteroneocystomy. Fistulae have been reported in up to 4% of repairs. Till date, follow up of the two operated patients is excellent. Both of them are doing well, and in our case, we can say that success is 100%. However, it is very difficult to presume such findings so early as it requires more number of patients to actually calculate the success rate of the operative procedure.[12]

On follow up, the patient was followed after 3 months, and almost all patients experienced improved symptoms, and all had reduced creatinine values compared to preoperatively.

CONCLUSION

Obstruction of the renal transplant should be promptly diagnosed and treated. PCN is a safe and effective method for immediate relief of ureteric obstruction. Balloon dilatation and ureteric stent insertion have a good technical success rate and outcome. In failed cases, the ultimate option remains the surgical procedure. After the study, we can also conclude that the management of the postrenal transplant stricture had a paradigm shift. Nowadays we are in more favour of minimally invasive procedure and endoscopic procedure rather than surgical intervention.

Disclaimers

The views expressed in the submitted article are the authors' own and not an official position of the institution or funder.

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Consent to publication statement

The authors declared taking consent for publication of the patient.

Ethical statement

The authors declared that they followed ICMJE authorship criteria and approved the final version of the manuscript. A signed authorship declaration form has been submitted to the editorial office.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Can quantitative monitoring of B cells evaluate the efficacy of Rituximab in primary CNS demyelinating disorders?

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Abstract

Introduction: Rituximab (RTX), initially approved for various blood cancers, is additionally used for the management of primary central nervous system (CNS) demyelinating disorders. This study aimed to quantify the % of B cells following RTX therapy in patients with primary CNS demyelinating disorders, so as to establish a correlation, if any, between the degree of B-cell depletion and clinical response(s).

Materials and Methods: A prospective, observational study was conducted from February 2020 to August 2021 in 15 adults diagnosed with primary CNS demyelinating disorders. The % of B cells was quantified in terms of CD20 by flow cytometry, and clinical evaluation was by Expanded Disability Status Scale (EDSS) scores. Following the first dose of RTX, the %CD20 counts were measured 2 and 24 weeks later; subsequently, depending on the %CD20, RTX was administered. Accordingly, patients were divided into Group 1 ($n = 7$, %CD20 ≥ 1.5) and Group 2 ($n = 8$, %CD20 < 1.5) and followed up on the basis of CD counts till the completion of the study or until they were lost to follow-up. Safety was evaluated by recording of treatment-emergent adverse drug reactions (ADR).

Results: In patients with CNS demyelinating disorders ($n = 15$), their median (interquartile range [IQR]) %CD20 and EDSS at baseline was 9.8 (5.6–18.8)% and 8.0 (7.5–8.0)%, respectively. In Group 1 ($n = 7$, %CD20 ≥ 1.5), there was a gradual decrease of %CD20 and EDSS, whereas in Group 2 ($n = 8$, %CD20 < 1.5), despite withholding RTX, patients remained asymptomatic, and their %CD20 remained <1.5 and EDSS showed a gradual decrease. 87% of patients experienced at least one ADR, the median (IQR) of ADRs per patient was 3 (0–3), and all 31 ADRs were infusion-related, with 100% recovery.

Conclusion: RTX was relatively safe to use in these disorders, and monitoring its efficacy was adequately achieved using EDSS, with no additional benefits accrued by measuring %CD20 counts.

Keywords: ADRs of Rituximab, CD20, primary CNS demyelinating disorders

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INTRODUCTION

Diseases like multiple sclerosis, neuromyelitis optica (NMO) (Devic's disease), diffuse cerebral sclerosis, and acute disseminated encephalomyelitis are termed primary central nervous system (CNS) demyelinating disorders[1] and share a common component of demyelination, defined as a

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process of myelin depletion. CNS demyelinating disorders can be classified into primary and secondary, where the former suggests the loss of myelin alone resulting either from the destruction of the myelin sheath or that of the cells that form and maintain myelin.[2] In cases of secondary CNS demyelination, there is myelin depletion following axonal injury.[2] Histologically, primary CNS demyelination displays the presence of abundant foamy KP1 macrophages containing myelin debris and lipid droplets, whereas the neurofilament-positive axons are spared.[2] The underlying mechanisms of demyelination range from mechanical compression[3,4], nutritional deficiency[5], myelinotoxic agents[6], viral infections,[7] or immunological causes.[8]

Rituximab (RTX) is a human/murine, chimeric, glycosylated immunoglobulin (Ig) G1-κ mAb containing murine light- and heavy-chain variable region sequences and human kappa and human IgG1 constant region sequences. RTX has a specific affinity for the B-lymphocyte transmembrane protein, CD20, which is expressed on normal B cells (excluding stem cells, pro-B cells, and plasma B cells) and on most malignant B cells.[9] RTX was initially approved in 1997 by the US FDA for the treatment of refractory or indolent non-Hodgkin's Lymphoma but has since come a long way in the field of modern medicine and is used in the management of rheumatological disorders[10,11], dermatological disorders[12], autoimmune hematological disorders[9], treatment of insulin resistance[13] and in more recent times, primary CNS demyelinating disorders.[14,15] The effectiveness of RTX in primary CNS demyelinating disorders is conventionally assessed by the Expanded Disability Status Scale (EDSS) score, i.e., clinical improvement. In this study, the effectiveness of measuring the %CD20 in circulation as a potential marker of monitoring the disease status was undertaken and compared with the EDSS score.

MATERIALS AND METHODS

A prospective observational study was conducted from February 2020 to August 2021 (18 months) in patients with primary CNS demyelinating disorders at Bangur Institute of Neurosciences (BIN), Annex 1, Institute of Post Graduate Medical Education and Research, IPGME&R and SSKM Hospital, Kolkata. In these patients, Flow cytometry for evaluation of %CD20 in peripheral blood was done in the Department of Pharmacology, IPGME&R, Kolkata.

Patients receiving maintenance RTX as a disease-modifying therapy for primary CNS demyelinating disorders were included. Pregnant or lactating females; patients with cardiac comorbidities; patients diagnosed with human immunodeficiency virus, hepatitis B, and hepatitis C; patients with unevaluated abdominal pain or having the risk of perforation; patients with untreated concurrent infections like respiratory or urinary tract infections and patients who had received recent vaccinations were excluded from the study. A review of past admission records at BIN indicated that annually, 8–10 subjects diagnosed with primary CNS demyelinating disorders presented at the "Demyelination clinic," suggesting that the study population is relatively small; accordingly, a formal statistical sample size calculation was not attempted. The study received approval from the Institutional Ethics Committee of IPGME&R, Kolkata (IPGMER/IEC/2020/362), and written informed consent was obtained. A structured case record form (CRF) was designed for data collection. Information regarding OPD consultation, admission, treatment modalities, blood test reports done at BIN, and the outcome of treatment was recorded.

Patients diagnosed with primary CNS demyelinating disorders (n = 15) were enrolled (NMO [n =13], multiple sclerosis [n =1], and autoimmune encephalitis, [n = 1]), and their %CD20 counts and EDSS scores evaluated at baseline, i.e., 0 weeks. Subsequently, RTX infusion (100 mg/h over 5 h) was administered at week 0, 2, and 24, and %CD20 and EDSS similarly evaluated along with a recording of adverse effects.

From the physician's point of view, at 24 weeks, patients were categorized into two groups based on their %CD20 count, i.e., Group 1: patients with a %CD20 > 1.5 (n = 7) and Group 2: patients having a %CD20 count ≤ 1.5 (n = 8). Patients in Group 1 additionally received RTX infusion at 26 weeks and were asked to report again 6 months later, i.e., 50 weeks. In Group 2, the %CD20 count was measured every 4 weeks, i.e., weeks 28, 32, and so on, and RTX was administered only when the %CD20 count was ≥1.5, and from that time point was asked to revisit after 24 weeks. The EDSS score was evaluated at every visit using the Kurtze EDSS by observing the pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual and cerebral (mental) functions of study subjects, a score of 0 suggested normal neurological status while a score of 10 meant death.[16]

Immunophenotyping

Whole blood (100 µL) stained with anti-human fluorescein isothiocyanate (FITC) conjugated anti-CD20 was incubated for 20 min; erythrocytes were lysed by incubating in BD Fix-lyse lysing buffer for 10 min (2 mL), washed twice with phosphate-buffered saline (0.02 M, pH 7.2, PBS) and finally resuspended in PBS (400 µL) for acquisition in a flow cytometer (BD Accuri™ C6 Plus, BD Biosciences, San Jose, CA, USA). Cells were initially gated on their characteristic

morphology of forward versus side scatter, following which B cells were identified as CD20-FITC positive; 10,000 cells were acquired per tube and analyzed using BD FACS Suite Software (BD Biosciences).

Statistical analysis

The study data were collected in a CRF and analyzed using GraphPad Prism Version 8.4.2 statistical software (GraphPad Software Inc., San Diego, CA, USA). All study variables, depending on the data type, were summarized using median (interquartile range [IQR]) and categorical variables expressed as percentages. The test for normality was done by the Shapiro-Wilk test. Inferential statistics for comparing data between various subgroups were done by Mann–Whitney test and Fisher's Exact test for sociodemographic and baseline characteristics between the two groups, and one-way analysis of variance through Kruskal–Wallis test and post-hoc analysis was done by Dunn's multiple comparison test. A *P*-value ≤0.05 was considered statistically significant, along with the 95% confidence interval for the test statistic was computed.

RESULTS

A prospective, observational study was conducted in patients diagnosed with primary CNS demyelinating disorders to assess whether monitoring of B cells following administration of RTX would be beneficial in evaluating its efficacy and safety. The efficacy was evaluated in terms of the %CD20 counts and EDSS scores, and the safety endpoint was evaluated by documenting the occurrence of treatment-emergent adverse events.

Study population

During the study period (February 2020 to August 2021, 18 months), 15 patients were enrolled and based on clinical and radiological findings were diagnosed with primary CNS demyelinating disorders.[17] Four patients had AQP4 positivity, and four had MOG positivity, whereas the status of the other seven were not known. These cases were resistant to conventional steroid therapy and were scheduled to receive RTX therapy. No additional immunosuppressive or corticosteroid therapy was conducted along with RTX infusion. There was a male preponderance, and the majority hailed from rural and semi-urban areas [Table 1]. Age-wise, 67% of the patients belonged to the 18–35 years category.

At recruitment, that is, baseline (week 0), the %CD20 counts were 9.8 (5.6–18.8)% at and were in the normal range (6%–23%)[18] [Table 1] while the Kurtzke Expanded disability status scale (EDSS) scores were 8.0 (7.5–8.0) [Table 1]. These patients received RTX (1000 mg, 100 mg/h, IV), and the %CD20 was again quantified at weeks 2 and 24 post-RTX. At week 2 and week 24, the %CD20, as compared to week 0, had decreased by 1.4 fold to 6.9 (4.3–11.5)% and by 6.5 fold to 1.5 (1.2–3.5)%, $P < 0.0001$, respectively. The EDSS scores measured at similar time points, namely weeks 2 and 24, were unaltered at week 2 being 8.0 (7.5–8.0), whereas at week 24 showed a 78% depletion, the EDSS score being 4.5 (4.0–6.0).

Table 1: Study population demographics

Parameter	*n* (%)	95% CI (%)
Gender		
Male	9 (60%)	35–85
Female	6 (40%)	15–64
Age (years)		
Range	18-52	
Mean ± SD	30.93 ± 11.65	
Age category (years)		
18–35	10 (67%)	43–91
36–59	5 (33%)	9–57
Above 60	0	0
Residential status		
Rural and semi-urban	11 (73%)	46–92
Urban	4 (27%)	4–49
%CD20 count		
Median	9.8	
IQR	5.6–18.8	
EDSS score		
Median	8.0	
IQR	7.5–8.0	

IQR: interquartile range, SD: standard deviation

Table 2: Intergroup comparison at 24 weeks

Parameters	Group 1 (*n* = 7)	Group 2 (*n* = 8)	*P*-value
*Age (years)	32.0 (24.0–50.0)	30.5 (22.8–44.0)	0.63
Gender, M:F	4:3	5:3	>0.99
*%CD20 count at 24 weeks	3.5 (1.8–4.5)	1.2 (1.0–1.4)	0.07
*EDSS score at 24 weeks	4.5 (3.5–5.5)	4.5 (3.6–5.9)	0.79

*All data are expressed as median (IQR)

Monitoring of %CD20 in Group 1

Based on the %CD20 count at 24 weeks, patients were subgrouped into Group 1 ($n = 7$, %CD20 ≥ 1.5) and Group 2 ($n = 8$, %CD20 < 1.5). There were no differences with regard to their age, gender, and EDSS scores, but the %CD20 was 3.0 fold lower in Group 2 *vis-a-vis* Group 1 [Table 2]. On an individual basis, in Group 1 ($n = 7$), at week 24, the %CD20 count remained ≥1.5% [Figure 1, i–vii], whereas in Group 2 ($n = 8$), the %CD20 count was consistently ≤1.5% [Figure 2, i–viii]. Taken together, in Group 1, the % CD20 at week 0 decreased at week 2 from 10.6 (6.6–18.8) to 6.9 (4.5–11.5), which translated into a decrease of 31.8% [Figure 1, viii]. Furthermore, at 24 weeks, the %CD20 further decreased by an additional 35.0% to 3.5 (1.8–4.5), $P < 0.0001$ [Figure 1, viii]. In terms of the EDSS scores measured serially, all the patients

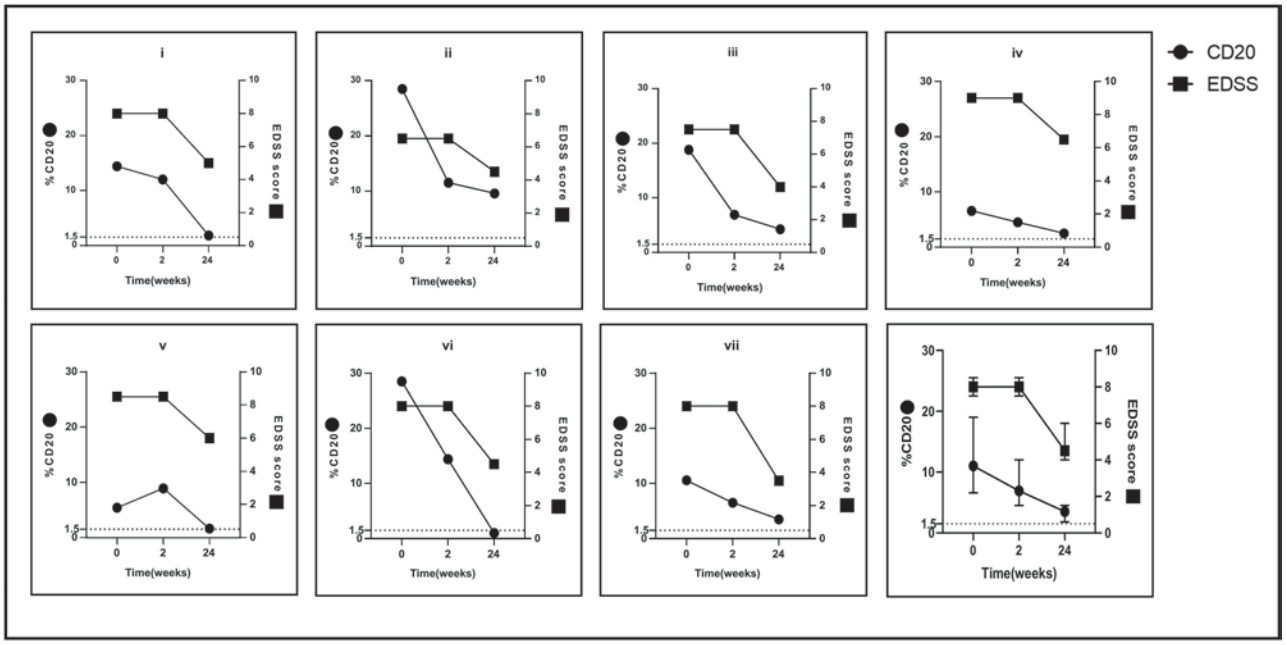

Figure 1: Serial monitoring over 24 weeks of %CD20 counts (●) and EDSS (■) in seven cases (Group 1) who were diagnosed with primary central nervous system demyelinating disorders whose %CD20 remained ≥1.5% as described in *Materials and Methods* section

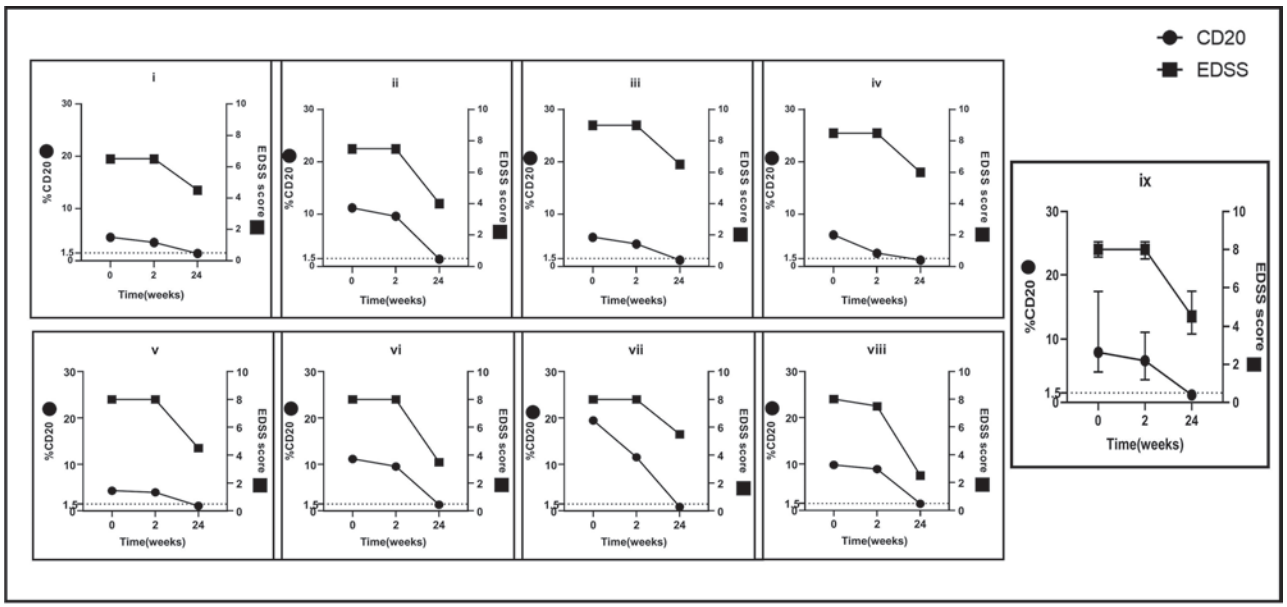

Figure 2: Serial monitoring over 24 weeks of %CD20 counts (●) and EDSS (■) in seven cases (Group 2) who were diagnosed with primary central nervous system demyelinating disorders whose %CD20 remained ≤ 1.5% as described in *Materials and Methods* section

in Group 1 showed no change between weeks 0 and 2 [Figure 1, i–vii], collectively being 8.0 (6.5–8.0) and 8.0 (6.5–8.0), respectively [Figure 1, viii]. However, at 24 weeks, in all seven cases, it consistently decreased to 4.5 (3.5–5.5), which represented a 40% decrease, $P < 0.0001$ [Figure 1, viii].

In Group 2, at weeks 0 and 2, the %CD20 decreased from 7.9 (4.8–17.4) to 6.6 (3.6–11.1), which translated into a % change of 22.7%; furthermore, at week 24, there was an additional decrease of 60% to 1.2 (1.0–1.4), $P < 0.0001$ [Figure 2, ix]. There was no change in the EDSS score between weeks 0 and 2 [Figure 2, i–viii], being 8.0 (7.6–8.4) and 8.0 (7.5–8.4), respectively [Figure 2, ix]; however, at week 24, all eight cases demonstrated a decrease [Figure 2, i–viii], collectively translating into a 37.5% decrease to 4.5 (3.6–5.9), $P < 0.0001$ [Figure 2, ix].

In view of patients in Group 1 at week 24, having a %CD20 ≥1.5%, patients received RTX at weeks 24 and

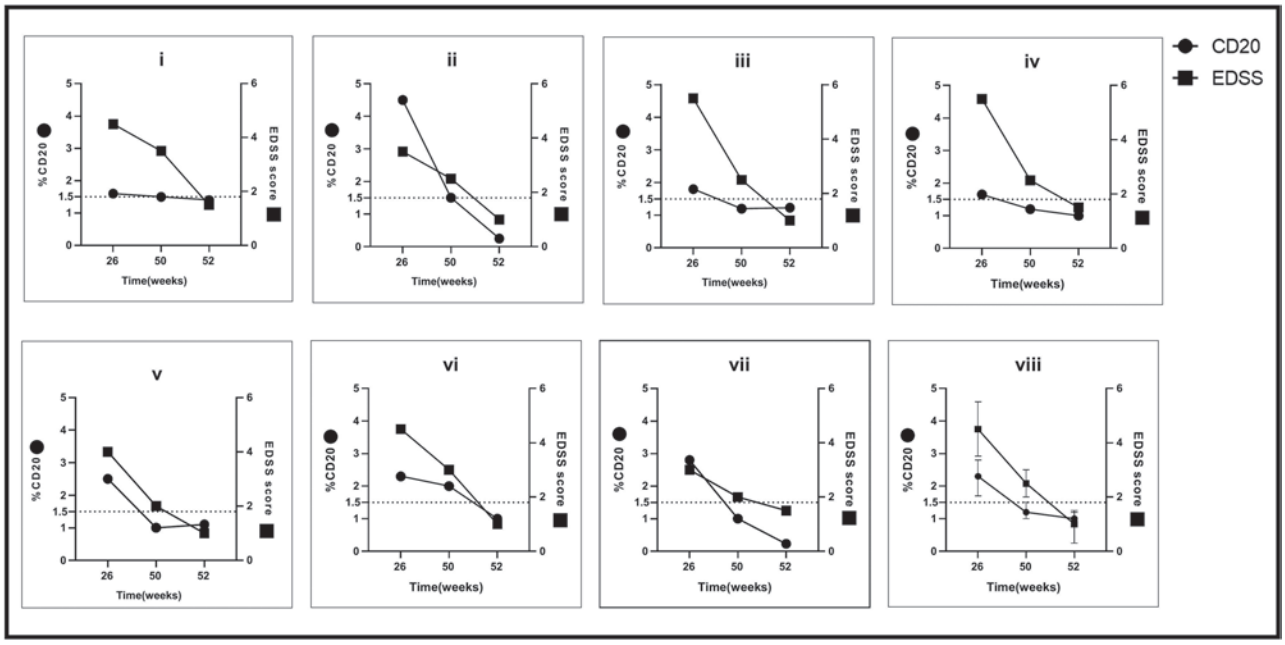

Figure 3: Serial monitoring at 26, 50, and 52 weeks of %CD20 counts (●) and EDSS (■) in seven cases (Group 1) who were diagnosed with primary central nervous system demyelinating disorders whose %CD20 remained ≥1.5% as described in *Materials and Methods* section

26. At week 26, all cases continued to have a count ≥1.5% [Figure 3, i–vii], while at week 50, 4/7 cases showed a depletion in their %CD20 to ≤1.5 [Figure 3, i–iv]. Overall, the %CD20 at 26 weeks decreased to 2.3(1.7–2.8)%, and at week 50, the %CD20 showed a further 1.9 fold depletion, being 1.2 (1.0–1.5)% [Figure 3, viii]. However, 2 weeks later, i.e., at week 52, in all cases, the %CD20 had decreased to ≤1.5, being 1.0 (0.3–1.2)%, [Figure 3, i–viii]. The EDSS measured at these time points indicated a steady decrease in all cases [Figure 3, i–vii], as scores at weeks 26, 50, and 52 were collectively 4.5 (3.5–5.5), 2.5 (2.0–3.0), and 1.0 (1.0–1.5), respectively [Figure 3, viii].

In Group 2 (n = 8), at week 24, the %CD 20 remained ≤1.5; RTX was withheld, and patients were asked to report at week 28. At week 28, in 5/8 cases, the %CD20 remained ≤1.5 [Figure 4, i–v], and were asked to report after 4 weeks. Amongst these five cases, at week 32, 3/5 [Figure 4, i, iv, v] continued to have a %CD20 ≤1.5 and were asked to return after 4 weeks, i.e., week 36; among these three, at week 36, 2/3 [Figure 4, i, v] continued to have a %CD20 ≤1.5, and were asked to return after 4 weeks, i.e., week 40. At week 40, only one patient [Figure 4, v] continued to have a %CD20 ≤1.5, whereas one was lost to follow-up [Figure 4, i]. On the other hand, in the remaining 3/8, whose %CD20 at week 28 increased to ≥1.5 [Figure 4, vi–viii], they were asked to return at week 52; only one continued to have a %CD 20 ≥1.5 [Figure 4, vii], whereas in 2/3 their %CD20 had decreased to ≤1.5 [Figure 4, vi, viii]. Although there was substantial variation in the %CD20 counts [Figure 4, i–viii], the EDSS remained unchanged or demonstrated a consistent, steady decline [Figure 4, i–viii].

Additionally, an MRI of the orbits and brain showed typical features of optic neuritis with hyperintense and atrophied optic nerves on T2-weighted sequences, bilateral optic nerve involvement, and extension of the abnormal signal posteriorly as far as the chiasm (suggestive of NMO). MRI of the brain revealed lesions in the periventricular white matter, periaqueductal grey matter, hypothalamus, dorsal pons, medulla, and corpus callosum. With RTX therapy, the MRI findings improved substantially but not completely. The MRI findings followed a consistent improving pattern in spite of variable changes in CD20 counts.

Adverse drug reactions (ADRs) were documented in the study at every visit. Out of a total of 15 patients, 13 (86.6%) experienced infusion-related ADRs [Table 3]. All the 31 ADRs reported were listed in the prescribing literature, and no new, unreported ADR was stated. Of the infusion-related ADRs, there were infusion-related chills, rigor, and fever. Although the patients received prophylactic promethazine, the incidence of infusion-related ADRs was high. All ADRs were managed conservatively with intravenous hydrocortisone 100 mg and temporary stoppage of infusion. There were no cases of anaphylaxis or skin rashes. In patients of Group 2, where the drug was withheld due to a low %CD20 count, no reports of ADRs were stated.

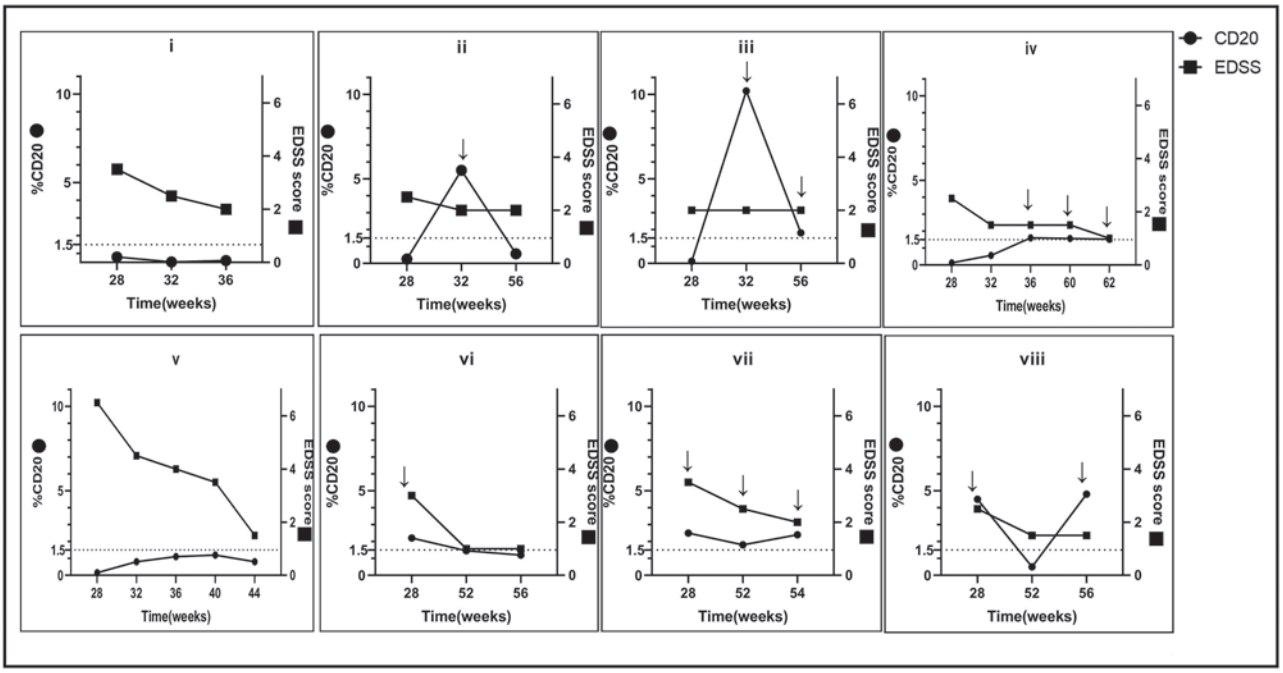

Figure 4: Serial monitoring beyond 24 weeks of %CD20 counts (●) and EDSS (■) in eight cases (Group 2) who were diagnosed with primary central nervous system demyelinating disorders whose %CD20 remained ≤1.5% as described in *Materials and Methods* section. Rituximab was administered at time points (designated by ↓) where %CD20 counts went ≥1.5%

Table 3: ADRs reported with Rituximab during the study protocol

Total number of ADRs	31
Number of patients who had at least one ADR *n* (%)	13 (87%)
ADR per patient	
Range	0–3
Number of serious ADRs	0
The outcome of individual ADR	
Recovered	31 (100%)
Death	0

DISCUSSION

In patients with primary CNS demyelinating disorders, repeated and grave clinical relapses bring about disabilities like permanent blindness, movement disorders, and problems in sphincter functions like urinary retention, inadequate passage of stool, or even constipation.[19] The frequency and severity of disabilities are directly proportional to the number of relapses, which add to the burden of destructive multifocal inflammatory lesions. Therefore, the ideal management of these cases should aim to reduce the number of relapses, which usually require immunosuppressive agents. As of now, no clear-cut treatment guidelines are available; azathioprine (AZA) and mycophenolate mofetil (MYC) have been tried with some success, as a reduced relapse rate and disability have been reported.[20-23]

RTX is used for the treatment of CNS demyelinating disorders, especially NMO[24], and a significant reduction of relapses and improvement in EDSS scores have been reported.[25-30] RTX has been extensively used in patients with NMO, NMO spectrum disorders, autoimmune encephalitis, multiple sclerosis, and other CNS demyelinating disorders, especially in those resistant to drugs like AZA, MYC, or methylprednisolone. In this study, RTX was the second-line therapy to those who were previously on AZA, MYC, and oral corticosteroids and as first-line therapy to two patients who had severe forms of NMO with both myelitis and optic neuritis.

A major gap in the current knowledge of RTX treatment of primary CNS demyelinating disorders is the dosing schedule for these patients. Considering the cost and limited safety data in patients diagnosed with primary CNS demyelinating disorders, a strategy to monitor therapy could be beneficial. In this study, irrespective of the grouping, with 24 weeks of treatment, there was a significant reduction ($P < 0.0001$) in %CD20 counts and EDSS scores in all 15 patients [Figures 1, 2]. However, thereafter, there were varied responses in %CD20 counts over time in both groups, i.e., Groups 1 [Figure 3] and 2 [Figure 4]. However, the EDSS scores showed a steady decline over time, in congruence with previous studies. With the reduction in EDSS scores, a reduction of disabilities was noted, indicating that monitoring of RTX with a clinical tool, i.e., EDSS scores was an excellent monitoring tool, and no additional advantage was accrued by monitoring the depletion of CD20 by flow cytometry.

The need for observing the annual relapse rate is crucial in determining the treatment outcomes and also in evaluating sustained efficacy and long-term tolerability. Due to logistic limitations, the COVID-19 pandemic, and limited resources in our study setting, we could not monitor the patients over a longer period of time. The long-term use of RTX showed a reasonable safety profile. Risks of progressive multifocal encephalopathy, malignancies, and severe infections have been noted,[31] but in our study, there were no such complications. Except for instances of infusion-related reactions like fever, chills, and rigor in 13/15 patients, there were no serious adverse events during RTX therapy. Moreover, the adverse effects weaned off from the second cycle of therapy in these 13 patients, indicating that in patients with primary CNS demyelinating disorders, RTX has an acceptable safety profile.

Our study had limitations in that enrollment of a large number of subjects with primary CNS demyelinating disorders on RTX therapy was limited, attributable to it being a single-center study performed during the COVID-19 epidemic and time constraints. Multicenter studies with large sample sizes would have given better and more robust results. However, to the best of our knowledge, this is the first study from Eastern India that endorsed the safety and efficacy of RTX in patients with primary CNS demyelinating disorders.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Conscious sedation in pediatric dental procedures: Experience from Usmanu Danfodiyo University Teaching Hospital, Sokoto, Northwestern Nigeria

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Abstract

Background: The management of fear and anxiety in children scheduled for dental procedures has been a great challenge to the operating dental surgeon. Despite several controversies regarding the effectiveness, and safety of conscious sedation in dental and minor oral surgical procedures, it is widely used nowadays in dental practice. This study aimed to present a retrospective analysis of pediatric dental patients managed under conscious sedation.

Materials and Methods: This was a retrospective study conducted over 5 years. After obtaining ethical approval from the research and ethics committee of the institution, the case records of all patients from 15 years and below who had a dental procedure under conscious sedation were retrieved. The demographics, procedures performed, the drug and dosage used, and length of the procedure were also recorded. Data obtained were analyzed using a statistical package for social sciences (IBM SPSS) version 25.

Results: A total of 196 patients were included, 92 (46.9%) males and 104 (53.1%) females in the age range of 1–14 years and mean ± SD of 6.79 ± 2.98 years. The age categories were analyzed against the gender which revealed more female children between 6 and 10 years with no statistically significant difference ($\chi^2 = 4.566$; df = 2; $P = 0.102$). The conscious sedation was done with ketamine 1–2 mg/kg intravenously in 72 patients (36.7%) and 3–4 mg/kg intramuscularly in 124 patients (63.3%), and additional doses were given in 93 patients (47.4%). Pulpectomy only constitutes the highest procedure performed in 42 patients (21.4%). The range length of the procedures was 5–67 min. Multiple procedures were performed in 52 (26.5%) of the patients. All patients were monitored until complete recovery, and no complications were recorded.

Conclusion: Conscious sedation with ketamine was found effective and safe during dental and minor oral surgical procedures. With good functional suction, conscious sedation can provide excellent patient cooperation in carrying out multiple procedures in pediatric dental patients.

Keywords: Conscious sedation, extraction, ketamine, pulpectomy, pulpotomy

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INTRODUCTION

Conscious sedation has been defined as a drug-induced depression of consciousness where the patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation.[1] Conscious sedations serve as a way to administer dental treatment comfortably to uncooperative patient who requires dental treatment.[2] The indications for conscious sedation include dental phobia, and anxiety, trauma, long dental procedures in children, medical conditions aggravated by angina, asthma, epilepsy, children more than 1 year, mentally challenged individuals, and ineffective local anesthesia due to any reason.[3] A wide range of agents have been used to administer conscious sedation, each with its merit and demerit. These agents include nitrous oxide, ketamine, propofol, sevoflurane, benzodiazepines such as midazolam, and opioids such as fentanyl.[4] To gain the maximum and safe benefits from performing dental procedures under conscious sedation, patients' evaluation with respect to airways, fasting, and understanding of the pharmacodynamics and pharmacokinetics of the drug to be used must be established. Additionally, a good suction device, airway management apparatus, patent venous access, and appropriate intraoperative and recovery monitoring are also essential.[5,6] This study aimed to present a retrospective analysis of pediatric dental patients managed under conscious sedation using intramuscular and intravenous ketamine. This study has provided insight into the safety and effectiveness of conscious sedation in a dental clinic setting.

MATERIALS AND METHODS

This was a retrospective study conducted at Usmanu Danfodiyo University Teaching Hospital, Sokoto State Nigeria, over 5 years (March 2018 to March 2023). Ethical approval was obtained from the research and ethics committee of the institution with reference UDUTH/HREC/2022/1144/VI. All pediatric patients' case notes who had dental procedures under conscious sedation in the dental clinic during the study period were retrieved. The demographics of the patient including age and sex were recorded. The procedures performed, the drug and dosage used in the conscious sedation, and length of the procedure were also recorded. Data obtained were analyzed using a statistical package for social sciences (IBM SPSS) version 25.

RESULTS

A total of 196 patients were treated under conscious sedation during the study period and there were 92 (46.9%) male and 104 (53.1%) female children in the age range of 1–14 years and gender which revealed more female children between 6 and 10 years with no statistically significant difference (χ^2 = 4.566; df = 2; P = 0.102) [Figure 1 and Table 1]. All patients were normal children with no underline medical or developmental condition. The conscious sedation was done with a ketamine 1–2mg/kg intravenously in 72 (36.7%) and 3–4 mg/kg intramuscularly in 124 (63.3%) and additional doses were given in 93 (47.4%). Pulpectomy only constitutes the highest procedure performed 42 (21.4%) followed by dental extraction alone in 40 (20.4%) of the study patients [Table 2]. The range length of the procedures was 5–67 min. Multiple procedure was performed in 52 (26.5%) of the patients [Figure 2]. All patients were monitored with a pulse oximeter until complete recovery, and no complication was recorded.

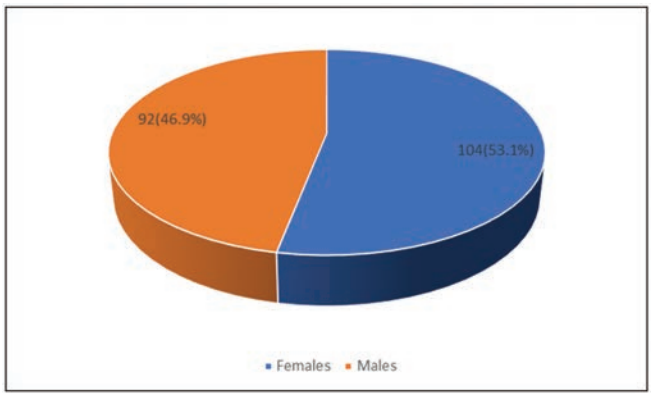

Figure 1: Sex distribution of the study population

Table 1: Analysis of gender against the age categories

Age category	Below 6 years	6–10 years	Above 10 years	Total
Sex				
Male	36	48	8	92
Female	26	68	10	104
Total	62	116	18	196 (100%)

Table 2: Frequency of procedures performed under conscious sedation

Procedure	Frequency (%)
Glass ionomer cement restoration (GIC)	30 (15.3)
Pulpotomy only	17 (8.7)
Pulpectomy only	42 (21.4)
Stainless steel crown insertion	1 (0.5)
Root canal therapy	8 (4.1)
Pulpectomy + GIC	4 (2.0)
Pulpotomy + GIC	7 (3.6)
Pulpectomy + GIC + Extraction	1 (0.5)
Extraction only	40 (20.4)
Biopsy	28 (14.3)
Suturing	12 (6.1)
Plate removal	1 (0.5)
Splinting	2 (1.0)
Stainless steel crown insertion	1 (0.5)
Total	196 (100%)

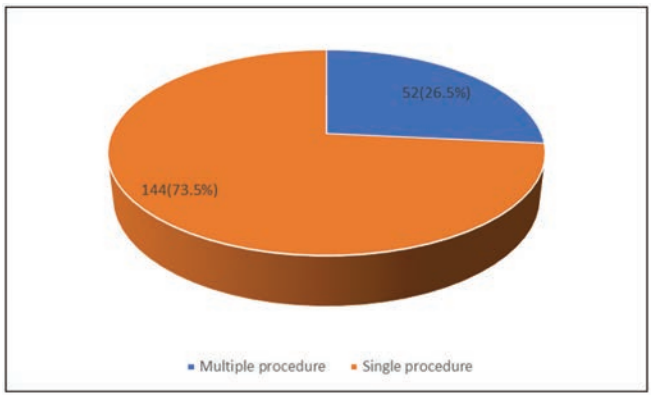

Figure 2: Distribution of procedures performed in each patient in to single or multiple

DISCUSSION

Anxiety and pain control constitute an integral part of dental practice and techniques to mitigate this should be explored. All patients deserve appropriate anxiety and pain control for any dental procedure. Fear and anxiety about dental treatment have been common among children. This study explored the analysis of conscious sedation used in children in the age range of 1–14 years. Although conscious sedation in dentistry is indicated in all age groups depending on the psychological parameters as well anxiety level, the majority of the reports are on children under the age of 16 years.[1,7,8] Children are less likely to cooperate during dental procedures due to fear and anxiety, especially with regard to invasive procedures. The highest uncooperative tendency that warrants giving conscious sedation was found in children in the age category of 6–10 years. Some children may show negative behaviors even with dental examinations. The female children appeared to be more anxious than male children as earlier reported by some authors.[9,10] This could be the reason for the higher frequency of conscious sedation in female children in this study.

There are several available pharmacological agents that could be used for conscious sedation.[1,11] These include nitrous oxide, propofol, sevoflurane, ketamine, and benzodiazepines such as midazolam. Ketamine 1–2 mg/kg intravenously and 3–4 mg/kg intramuscularly has been used I all the patients in this study.[11,12] Ketamine given in this dose was found to give good analgesia and safer adequate levels of sedation.[13] The most commonly reported untoward event related to ketamine by previous literature is what is called the emergence phenomenon (distinct pattern and behavioral changes caused by delirium).[14] This has been observed in about half of the patients in this study and has not in any way proven to be dangerous provided the patients are kept in a safety recovery environment. Ketamine was also documented to cause an increase in salivary and tracheobronchial mucus gland secretions, necessitating the use of an antisialagogue such as atropine before its administration.[15] Antisialagogue reduces the emetic side effect of ketamine producing an incidence of vomiting in 10% of children.[16]

The main challenges of conscious sedation in dental procedures are the sheared airway between the dentist and anesthesiologist.[1] To maximize safety, a good suction was available for all procedures. Patient selection is also very important. For example, a patient with an intraoral mass in which the site of incision is located where there is poor access to suction may not be feasible for conscious sedation.

Several pediatric dental procedures such as glass ionomer cement restoration (GIC), pulpotomy, pulpectomy, stainless steel crown, and some minor oral surgical procedures such as dental extraction, biopsy, and splinting can be performed effectively under conscious sedation.[3] Although some level of behavior management strategies could be applied and produce positive results in patients needing certain noninvasive dental procedures like GIC, some invasive dental procedures like extractions and pulpectomies were procedures that instill negative behavior and may require conscious sedation.

In conscious sedation, the pain sensations are abolished but are aware of what is going on around them.[17,18] As an advantage of conscious sedation, the adverse effects that could be associated with general anesthesia are avoided. Moreover, patients maintain their natural physiological reflexes and are capable of spontaneous breathing. Conscious sedation saves operators time and also permits multiple dental procedures in one visit and also saves the cost of admission and general anesthesia and lessens the stress of a longer hospital stay to the caregiver.

CONCLUSION

Conscious sedation is an effective way of dealing with fear and anxiety in dental treatment. ketamine was found effective and safe during dental and minor oral surgical procedures. With good functional suction, conscious sedation can provide excellent patient cooperation in carrying out multiple procedures in pediatric dental patients.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Deceased donor skin banking for making use of cadaveric skin as a temporary coverage: A life saving option to the patients with extensive burn injuries

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Abstract

Background: In India, xenografts are not available yet and biosynthetic skin substitutes are unaffordable to most of people. Deceased donor skin could be a lifesaving option for the victims with extensive burn injuries. The first deceased donor skin bank of eastern India was established at the Department of Plastic Surgery of a tertiary burn referral center, Kolkata on 22nd April 2013 for processing, storage, and utilization of donors' skin.
Aim: The aim of this study was to evaluate the advantages and importance of skin banking in terms of clinical outcomes based on retrospective data.
Materials and Methods: All deceased skin harvesting was carried out under a hospital setup. Out of 56 skin donations, 17 skin harvesting was performed on the whole donated body and 39 deceased skins were harvested from the brain death declared cases.
The outcome of skin banking and its utilizations was analyzed from our record of ten years.
Result: From April 2013 to April 2023, only 56 deceased skin donations were received. Number of the skin donations has increased especially in 2018 when the Regional Organ & Tissue Transplantation Organization (ROTTO, Eastern Zone) came forward with a structured organ donation program.
Harvested skins were utilized for 72 patients with extensive burn injuries. We observed partial adherence of cadaveric skin allografts over the wounds for 2–3 weeks. Fifty-five cases were free from infection and the conditions were beneficial for further autologous split-thickness skin grafting (STSG) in the second phase.
Conclusion: Temporary coverage for an extensive burn injury is extremely important and beneficial, in such cases cadaveric skin could be a potentially lifesaving option with desirable clinical outcomes. Common people are gradually accepting the concept of skin donation after death, however, more awareness programs and proper counseling are essential to make the mission of the skin bank successful. This field is still virgin and open for loads of R&D.

Keywords: Cadaver skin allograft, clinical outcome, skin bank

Key Message: Skin banking is essential for a tertiary burn care center. Temporarily, early coverage of extensive burn wounds with cadaveric skin graft improves clinical outcomes, mortality, and morbidity of the patients

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INTRODUCTION

Globally estimated annual death rate due to burns is over 180000 and the majority of them occur in low and middle-income countries, as reported by WHO.[1] With the introduction of newer concepts, facilities, and treatment options, survival probability improved from LA50 (Lethal Area 50) of 35% total body surface area (TBSA) in 1989 to LA50 of 50% TBSA in 1997.[2] However, the recent scenario has not improved much, as nearly 80% mortality rate has been reported for 40-50% TBSA in several studies.[3-6]

Early coverage for a burn wound is extremely important and cadaveric skin grafts are a good choice in such cases. In India, the importance of skin banks was realized long back and the first skin bank was inaugurated in Mumbai, on April 24, 2000[7], decades later the only skin bank in eastern India was started on April 22, 2013, under the department of H&FW, Govt. of W.B.

This article takes an account of the response of society to this newer concept of skin donation and banking. We have shared our experiences of utilization of cadaveric skin grafts, and its outcome over the timeline of the last 10 years.

MATERIALS AND METHODS

The skin bank was set up in accordance with the provision laid down in the Transplantation of Human Organ Act 1994 under the state appropriate Authority of the Government of West Bengal.

Cadaveric skin harvesting: Retrieval of skin from whole body donation is usually performed within 8–10 h after death and essentially prior to any chemical treatment for preservation and in case of organ donation skin was retrieved preferably within 4-6 hours after getting consent from the appropriate authority. Usually, superficial layers of the skin are retrieved from both side of the thighs and back of the deceased body which does not lead to any bleeding and disfigurements. However, harvesting can be done even after 6 hours if the body maintains cold temperature because the primary aim of a cadaveric skin graft is to cover the wound for a temporary period. The process of harvesting requires hardly 30 minutes and immunological matching between donor and recipient is not essential.

Exclusion criteria: Skin should not be collected from a person who had pre-existing evidence of either HIV, HBsAg, Skin disease, Cancer, STD, Severe infection or had taken steroids for a prolonged time.

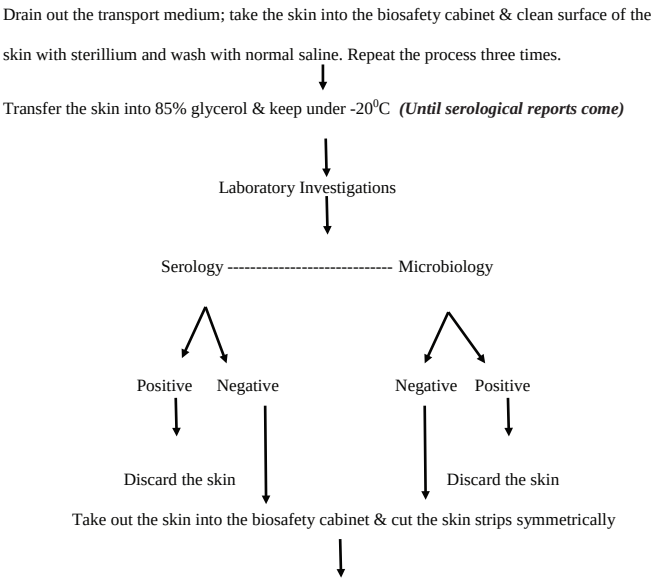
Inclusion criteria: Potential donors from any age group and sex are acceptable.

Transport of collected samples: Harvested skins must be immersed in 50% glycerol (transport medium) immediately and the sample container should be transported to the skin bank as early as possible. The process is not necessarily temperature-dependedependent.

Flowchart of the standard operating procedure for the processing & storage of the harvested skin

Drain out the transport medium; take the skin into the biosafety cabinet and clean surface of the skin with sterillium and wash with normal saline. Repeat the process three times.

Transfer the skin to 85% glycerol and keep it under -20°C (Until serological reports come)



Put the strips into the storage container with fresh 85% glycerol supplemented with 100 IU/mL penicillin and 100 µg/mL streptomycin Or 320 mg/L gentamicin and 500 mg/L vancomycin.

Level the storage box with identification number, date & time of preservation. Store the skin under -20°C until use.

Replace the storage medium at monthly intervals and repeat the microbial screening if not used within 6 months.

RESULTS

Response from the society

During the last 10 years, we have hardly received 56 skin donations. However, 89.28 % (50 out of 56) of such donations resulted during the last 6 years which is fairly encouraging, chronological data on skin donations during the last 10 years are shown in Table 1.

Seventeen skin allografts were harvested from the deceased body as a spontaneous response of our society towards whole body donation and since counseling for organ donation was started in early 2018 at our institute, 39 skin allografts have been harvested from the brain death declared persons so far [Figure 1].

Chronological data on donor's age distributions are shown in Figure 2 and the frequency distributions of donors' age depending on different age groups are presented in [Figure 3A] which shows majority of donors were more than 40 years. However, the median age group of the organ donors and whole-body donors are 45 years & 72 years respectively [Figure 3B] which indicates that the families of the young donors in spite of their heavily grief, are also coming forward for this noble cause to donate life after death.

Microbiological screening of cadaveric skin allografts

The frequency of positive culture from processed (but before preservation) skin allografts was only 3 (5.35%) while 53 out of 56 (94.65%) such skin allografts were negative for bacterial and fungal growth [Table 1]. Culture-positive skin allografts were not utilized.

We have performed a quality control study as well on the skin allografts which were not utilized within six months from the date of collection. Number of such remaining skin allografts (aged > 6 months) during 2017–2019 and in the year 2022 were 5, 3, 2, and 7, respectively, and reportedly, all such tested samples were negative for microbial cultures except 4 out of 7 (57.14%) samples of 2022 [Table 2], that seems to be an exceptional incident due to some unknown reasons.

Demographic of the recipients

Screened 49 skin allografts were utilized for a total of 72 burn victims. Grafts were randomly allocated among the patients. Out of 30 males, the adult-child ratio was 1:1, and out of 42 females, 22 patients were adult and 20 patients were children [Figure 4].

Clinical outcome

Of all 72 recipients, cadaver skin allografts were clinically examined on fourth postoperative day and advised for

Table 1: Chronological data showing frequency of skin donations and microbiological screening of preprocessed harvested cadaver skin samples

Frequency of skin donations (April 2013–April 2023)												
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	Total
N =	4	1	0	1	7	11	6	7	11	7	1	56
Culture Status	Frequency of positive culture reported for processed (but before preservation) cadaveric skin allografts											
Positive	1	0	0	0	0	1	0	0	1	0	0	3 (5.35 %)
Negative	3	1	0	1	7	10	6	7	10	7	1	53 (94.65%)

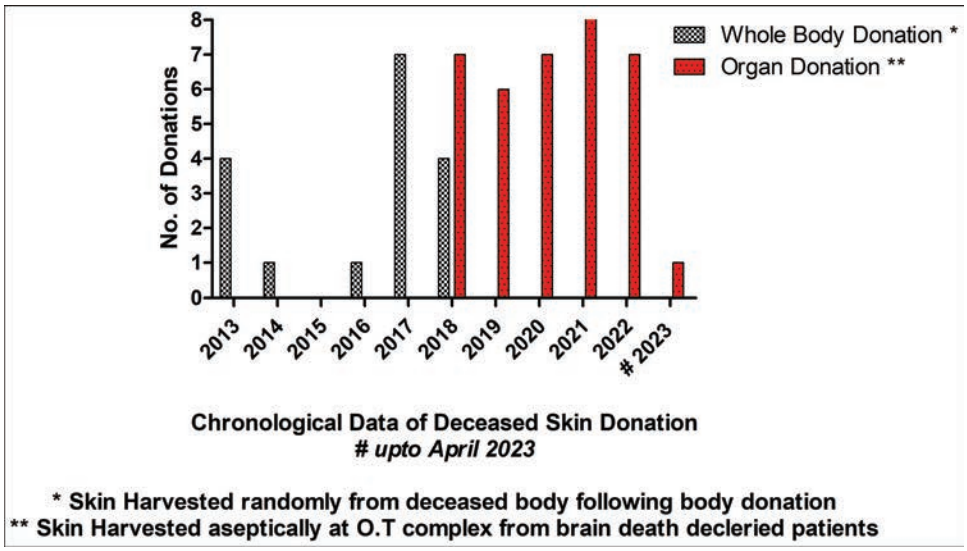


Figure 1: Chronological data on type of deceased skin donation (source of cadaveric skin)

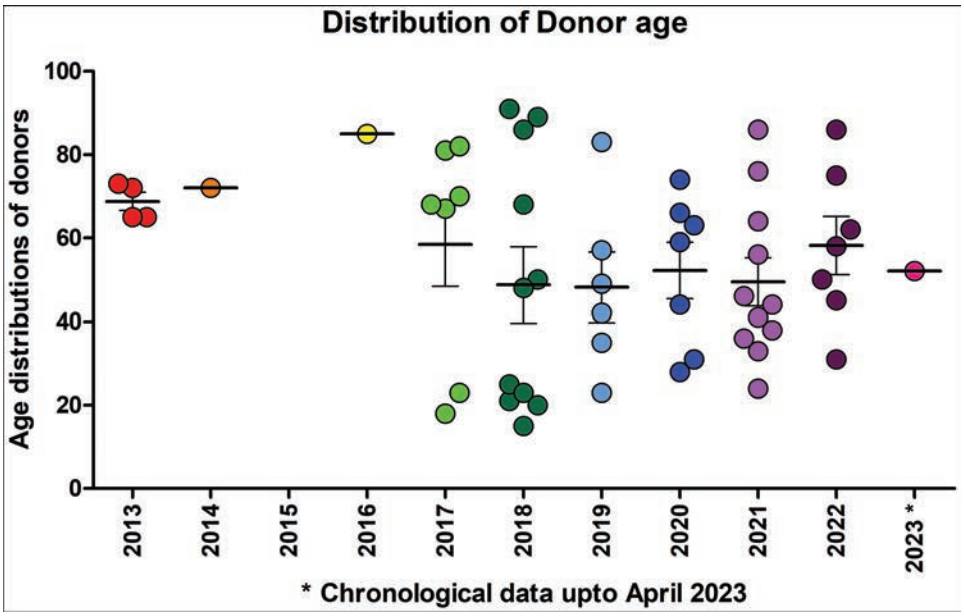


Figure 2: Chronological data on distribution of donors' age

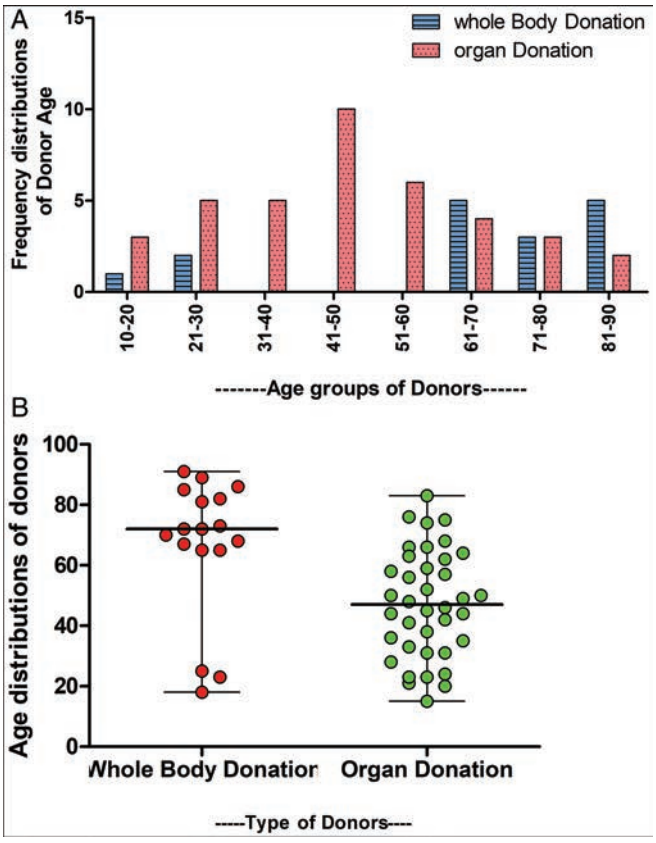


Figure 3: (A) Frequency distribution of donor age based on different age groups. (B) Age distributions of donors showing middle most (median) value along with the range between different donors groups (whole body/organ donation)

dressing change every alternate day. In 17 (23.6%) cases, wounds were found to be clinically infected. Clinical data for early rejection of cadaver skin allograft is shown in Table 3. Cadaver skin allografts served the purpose of temporary coverage of the wound for at least 2-3 post-operative weeks in 45 out of 72 (62.5%) cases.

However, 55 out of 72 cases subsequently underwent definitive STSG and among those 38 (69.09%) cases were successful [Table 3] which is encouraging.

DISCUSSIONS

When a wound requires STSG, usually it remains infected and thus is treated with systemic antibiotics as well as some topical prophylactic management is given. This procedure of controlling wound infection could easily take a period of 2 weeks which causes delay in planning for a definitive autologous STSG. Even though when operation takes place, it's completely uncertain whether the skin will take properly or not!

Furthermore while waiting for the wound to be prepared for the STSG, the patient continuously loses body fluids and protein reserve that leads to deterioration of patients general condition. Moreover, open wounds are always susceptible for new infection to occur.

To overcome these problems, human cadaver skin allografts could be a good option. Various studies have shown that new blood vessel can grow into the donor skin but more research work is required to establish this statement scientifically.[8]

However, data from our study with the success rate of 69.09% for cadaveric skin graft following a definitive (autologous) STSG [Table 3] is in well agreement with SA

Table 2: Microbiological screening of 6 months old cadaveric skin samples

Quality control: Screening of 6 months old (processed & preserved) cadaveric skin samples												
Culture status	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**Total**
N =	NA	NA	NA	NA	5	3	2	NA	NA	7	NA	17
Positive	0	0	0	0	0	0	0	0	0	4	0	4 (23.52 %)
Negative	0	0	0	0	5	3	2	0	0	3	0	13 (73.47 %)

NA = Not Applicable: Samples were preserved for < 6 months (utilized within 6 months)

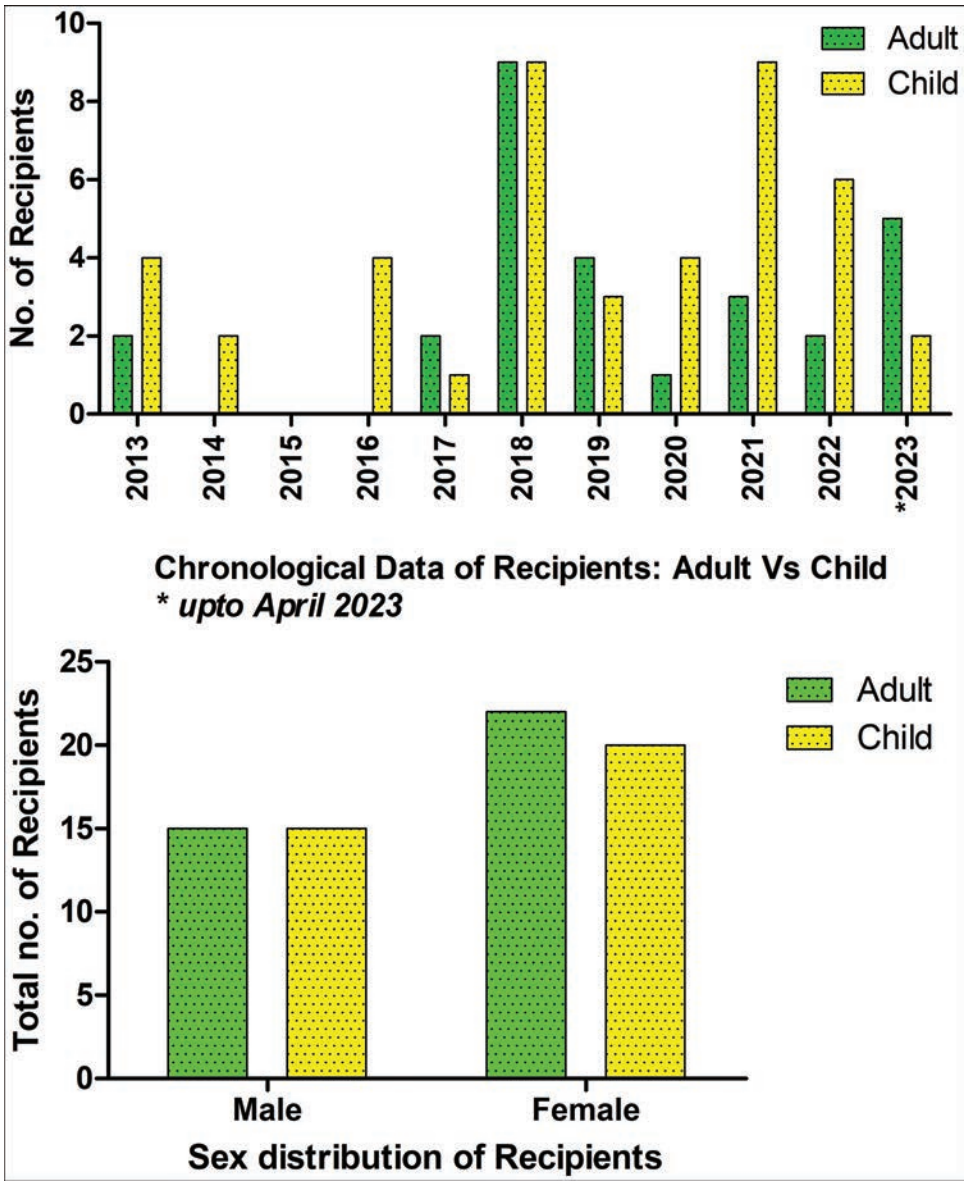


Figure 4: Sex distributions among recipients along with their respective adult and child proportions

Stegeman *et al.*[9] that the cadaver skin allograft as temporary coverage makes the wound ready and increases the chance of autologous skin take. To our opinion, this success rate is the resultant of early temporary coverage, even for the cases which had positive culture report. Clinically we have observed that general conditions of patients were improved well following temporary coverage with cadaver skin which on the other hand prevents new bacteria to enter at the wound site hence by limiting bacterial load, it improves the outcome of the antibiotics used.

Moreover, cadaver skin allograft could be the only option for the extensively burnt patient where availability of autologous skin is less. We had few patients who were given cadaver skin allograft harvested from healthy brain dead declared young persons. Four such patients had good

Table 3: Postoperative clinical outcome of cadaveric skin-grafting

Retrospective data on clinical outcome of Cadaveric Skin Grafting													
Periods——————>		**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**Total**
Wound infection	Yes	2	0	0	1	1	4	2	1	3	2	1	17 (23.6%)
	No	4	2	0	3	2	14	5	4	9	6	6	55 (76.4%)
Rejection of cadaveric skin grafts within the period of	1st Week	2	0	0	1	1	7	3	2	4	3	4	27 (37.5%)
	2nd Week	3	1	0	1	1	8	3	2	6	4	3	32 (44.44%)
	3rd Week	1	1	0	2	1	3	1	1	2	1	0	13 (18.05%)
Partial adherence	<4th Week	0	1	0	0	0	2	0	0	1	0	0	4 out of 72 (5.55%)
Graft take -successful autologous (definitive) STSG after cadaveric STSG	Yes	2	1	0	2	2	8	4	3	6	6	4	38 (69.09%)
	No	1	1	0	0	1	4	2	1	3	2	2	17 (30.9%)

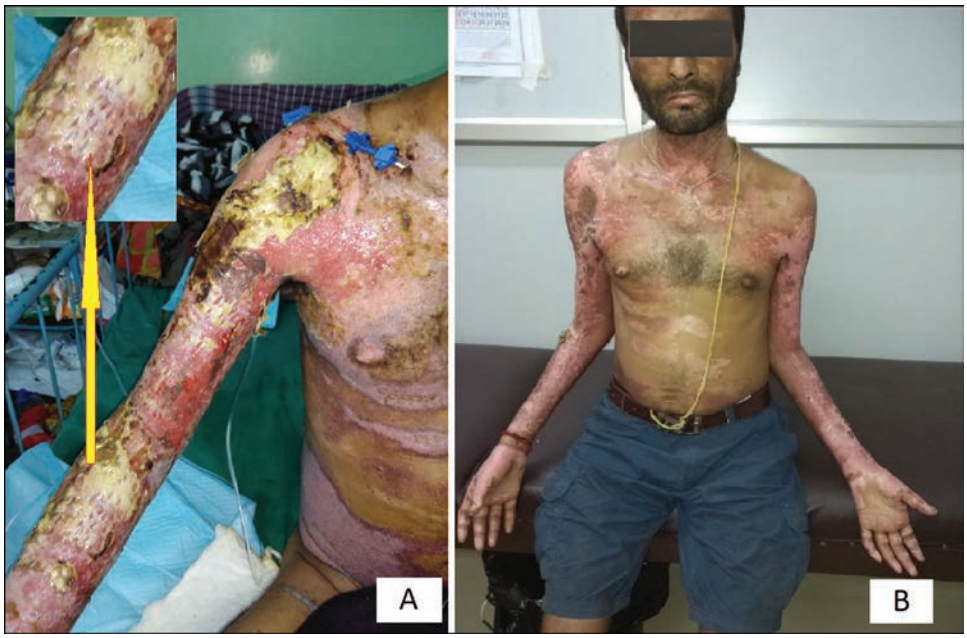


Figure 5: Partial adherence of cadaver skin allograft observed at third postoperative week (A). Condition of the wound after 2 months at OPD follow-up (B)

take [Figure 5] and all of them survived well. Though the numbers of such cases are only a few but it carries clinical importance. We need to perform more such cases to make definitive comment on this. At this point we can say cadaver skin allograft provides only benefits be it little or more but do not lead to any adverse event.

CONCLUSION

Early coverage of an extensive burn injury is extremely important and beneficial; cadaveric skin allograft could be a potential lifesaving option for such patients. It reduces chances for wound infection, and improves and prepare wound site early for a definitive autologous skin grafting. Controlled and comparative clinical trials need to be carried out with standard procedures to analyze the effectiveness and rate of success of using cadaveric skin grafts in a better way.

We have perceived the concept about the obvious benefits of cadaver skin allografts; though we have received only 56 skin donations in the last 10 years, encouragingly, encouragingly the frequency of donations is accelerated since our hospital-based counseling for organ donation started in 2018. Yearly, number of the skin donations is reflective of the response of our society to the concept of skin donation. During an early couple of years of skin banking, we used to receive whole-body donations only from elderly persons of more than 72 years of age (Median age group) but recently we have started receiving organ (Skin) donations from younger donors who fall under the median age group of 45 years. It reflects that probably our society has perceived the need for skin banking (Organ Donation).

However, more awareness program and proper counseling for organ donation is essential to make the mission of the skin bank successful. This fiel d is still virgin and open for loads of R&D to make the workflow of the skin bank more structured and utilization of the skin allografts more scientifically.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

An isolated case of pseudothrombocytopenia due to platelet satellitism with the review of literature

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Abstract

Platelet interaction with neutrophil polymorphs happens rarely, forming platelet aggregates like rosettes/beads around neutrophils, an uncommon phenomenon called 'platelet satellitism' (PS). It has been observed in peripheral blood smears prepared from blood samples anticoagulated with ethylene diamine tetra-acetic acid, but not in blood samples treated with heparin or sodium citrate. Automated hematology analyzers in present times have increased the reproducibility and accuracy of platelet counts, they may not completely resolve pseudothrombocytopenia. Being a rare cause of spurious thrombocytopenia, it might mislead the clinician into unnecessary investigations and treatment. To avoid false reporting of low platelet count, the peripheral blood smear examination should be performed in all patients with thrombocytopenia. PS usually occurs around neutrophil granulocytes and only in extremely rare cases are platelets phagocytosed by neutrophils, forming rosettes around lymphocytes and monocytes as observed only in patients with neoplastic lymphocytes. This study presents an isolated case of spurious thrombocytopenia due to PS around neutrophils, with platelet phagocytosis.

Keywords: Platelet satellitism, polymorphonuclear leukocytes, thrombocytopenia

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INTRODUCTION

Platelet satellitism (PS) is a rare *in vitro* phenomenon that occurs when an immunoglobulin G antibody directed against the glycoprotein IIb/IIIa complex on the platelet (PLT) membrane forms in ethylenediaminetetraacetic acid-treated peripheral blood at room temperature. Platelet satellitism occurs when an immunoglobulin G antibody directed against the glycoprotein IIb/IIIa complex on the platelet membrane forms in ethylenediaminetetraacetic acid-treated peripheral blood at room temperature. As the antibody coats the platelets, platelets adhering to polymorphonuclear leukocytes show a rosette-like appearance.[1]

It is not related to functional abnormalities of the blood, the patient's clinical condition, or to drug intake. The underlying mechanism of PS is not completely understood and there are a few studies trying to elucidate this PLT-leukocyte relationship.[2] References about PS in medical literature are few and not recent. There are only about 100 cases described although this phenomenon is much more frequent, indicating that PS is not recognized, or simply not reported.[3,4]

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CASE PRESENTATION

A 71-year-old man with a history of multiple joint pains for the last 2 months presented in the outpatient department of Regional Ayurveda Research Institute, Jammu. During routine baseline investigations, consent of the patient for blood sample collection was taken (as per routine). The whole blood sample collected in a tube with ethylene diamine tetra-acetic acid (EDTA) anticoagulant was analyzed in the Laboratory of RARI, Jammu, using a Hematology analyzer (ERBA H-560). The complete blood count (CBC) presented the following results: white blood cell, 4.20×10^3/uL; red blood cell (RBC), 3.65×10^6/uL; hemoglobin, 12.3 g/dL; hematocrit, 35.7%; MCV, 97.7 fl; mean corpuscular hemoglobin (MCH), 33.7 pg; MCH concentration, 34.4 g/dL; RBC distribution width, 12.7%; and PLT, 35×10^3/uL. Peripheral smear examination for PLT count was advised.

Blood smears were stained manually, using the Leishman stain. Following the execution of a CBC, a microscopic review of the peripheral blood smear was performed for essentially two reasons: both for the suspicion of pseudothrombocytopenia, and due to instrumental alarms referring to the PLT message as 'abnormal PLT distribution'. Blood smears were studied using light microscopy and the smear depicted features of PS. About 90% of neutrophils depicted features of PS with phagocytosis of PLTs in a few (20%).

Biochemical tests showed the following results: glucose (R), 284.4 mg/dL; aspartate aminotransferase, 21.9 U/L; alanine aminotransferase, 19.4 U/L; total bilirubin, 0.48 mg/dL; direct bilirubin, 0.13 mg/dL; indirect bilirubin, 0.35 mg/dL; urea, 27.70 mg/dL; creatinine, 0.88 mg/dL; uric acid, 5.29 mg/dL; calcium, 8.34 mg/dL; total protein, 7.3 g/dL; albumin, 4.5 g/dL; and globulin, 2.8 g/dL.

Previous clinical history

The patient was leading an active life following a vegetarian diet, with a history of diabetes for the last 20 years and an accident 50 years back with trauma to the vertebral column. The patient was on antidiabetic therapy. No other significant ailments were noted; however, the qualitative test for rheumatoid arthritis was positive during current investigations.

RESULTS

The blood cell count with differential cell count was performed on the automated hematology analyzer. The analyzer gave warning signals (flags) for thrombocytopenia and abnormal PLT distribution. It is after performing the blood smear analysis by light microscope that we noticed the PS. Most of the PMNs were surrounded by PLTs and leaned onto their membranes [Figure 1]. The satellitism was limited to blood samples anticoagulated with EDTA. Also, the PLTs seemed to adhere exclusively to PMN neutrophils with phagocytosis [Figure 2].

Interestingly, although PS has been reported as a cause of pseudothrombocytopenia, in our case, the PLT count showed very low levels, critical in terms of thrombocytopenia.

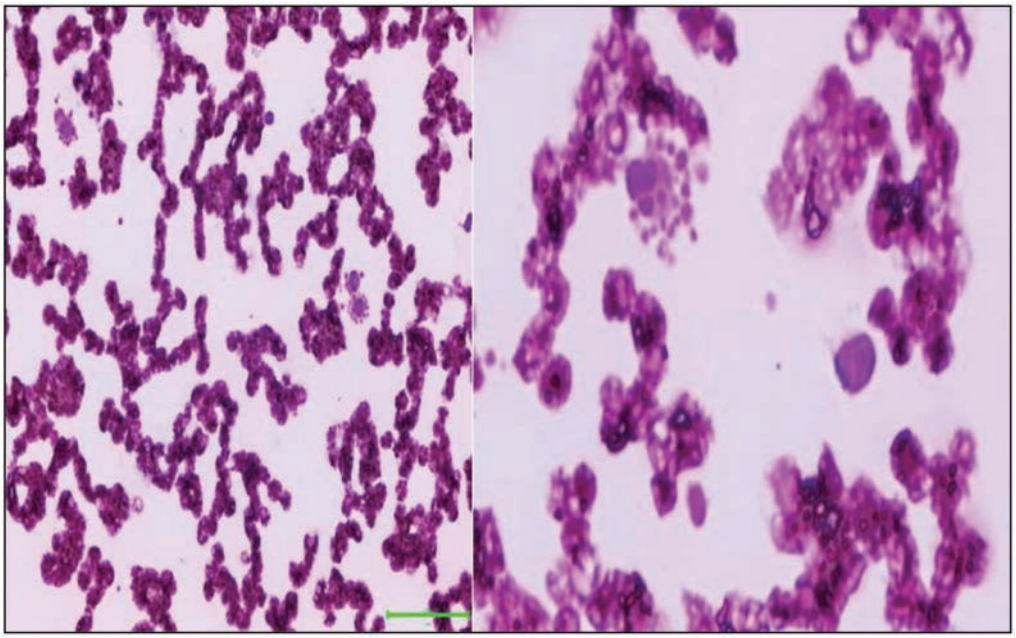

Figure 1: Platelet satellitism in blood samples anticoagulated with EDTA (40×)

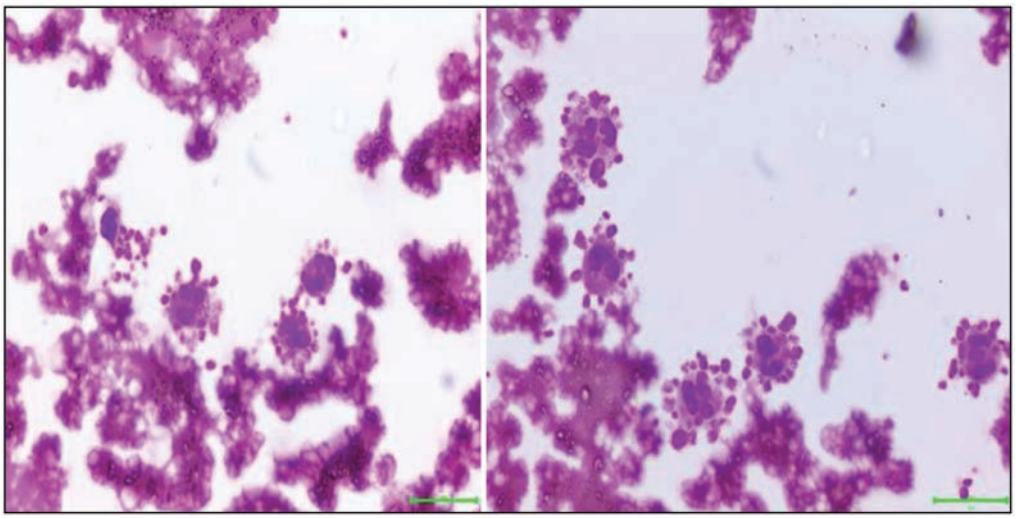

Figure 2: Platelet satellitism in neutrophils with phagocytosis(100×)

DISCUSSION

Lorubbio *et al.*[5] described PS around the three types of cells, that is, neutrophils, lymphocytes, and monocytes, and the interesting and rare finding of PLT phagocytosis in both the neutrophils and monocytes.

PS has been reported at any age; most individuals are asymptomatic and in various clinical states, such as pregnancy, autoimmune disorder, Behcet's disease, thromboembolism, chronic liver disease,[6,7] and malignant disorders like mantle cell lymphoma.[4] There have been previous reports of PS around neoplastic lymphoid cells,[8] large granular lymphocytes and monocyte-monocyte adhesion, satellitism, and phagocytosis of PLTs by monocytes without neutrophils being involved.[9,10] The cause may be immunological or nonimmunological. Severe rosetting may lead to a misdiagnosis of thrombocytopenia unless peripheral smears are examined.[6] Thus, recognition of this *in vitro* phenomenon re-emphasizes the necessity to execute the traditional and reliable peripheral blood film examination.

PS was first described in 1963 by Field and MacLeod as an incidental finding observed in the workup of thrombocytopenia caused *in vitro* by EDTA anticoagulation of blood at room temperature. It has been described in blood samples collected in EDTA only and not in anticoagulants such as heparin, citrate, acid-citrate dextrose, and ammonium oxalate. In 1986, Vondem Borne[11] introduced the idea of crypto-antigens or hidden antigens; according to an immunological mechanism, these antigens occur exclusively on PLTs, particularly on the membrane glycoprotein IIb/IIIa complex. These crypto-antigens are normally not exposed on circulating PLTs but are eventually exposed only when the PLT membrane passes through a conformational change as a result of Ca2+ ion removal by the chelator EDTA. Immunoglobulin G autoantibodies are directed against the binding complex formed between glycoprotein IIb/IIIa of the PLT membrane and the neutrophil Fc gamma receptor. A nonimmunologic mechanism has also been proposed, which claims that thrombospondin, or some other alpha-granule protein, is expressed on the PLT surface, facilitating adhesion to neutrophils in response to different processes.[12]

Kishore *et al.*[4] noted that in most cases of EDTA-dependent phenomena, effects on PLTs are greatest at room temperature or colder, and effects may even be eliminated if samples are kept at 37°C. Electron microscopy studies often help to corroborate light microscopic findings. Several studies have reported the formation of PLT dendrites and neutrophil pseudopods. Focal apposition of the plasma membranes of the two cell types with an interposed electron-lucent space is the most frequently observed form of contact.

Among the 14 patients with PS studied by Bizzaro *et al.*[10] in 1995, the presence of both EDTA-dependent anti-PLT and EDTA-dependent antineutrophil IgG (auto)antibodies was found in their sera. Antineutrophil activity was completely abolished when the sera were absorbed on normal PLTs, which suggests that a single antibody is involved. Inhibition studies with monoclonal antibodies indicated that this IgG autoantibody is directed against the glycoprotein IIb/IIIa complex of the PLT membrane, as well as the neutrophil Fc gamma receptor III (Fc gamma RIII).

PLT clumping can also occur in the presence of EDTA, and the PLT count again will be falsely decreased. The analyzer will probably flag the count for PLT clumps or giant PLTs.

If either PS or PLT clumping is observed on the peripheral smear, the sample could be recollected using sodium citrate as the anticoagulant. PLTs can then be counted using the automated method. The PLT count from a tube that contains liquid sodium citrate will need to be corrected for the dilutional effect of the citrate. This can be accomplished by multiplying the PLT count obtained from the automated analyzer by 1.1.

Bizzaro *et al.*[10] showed that, by incubating the PS patient sample with monoclonal antibodies anti-FcγRIII (CD16) and antiglycoprotein IIb/IIIa, the occurrence of PS can be completely blocked. They demonstrated also that no PS can be detected when PS-plasma was incubated with blood from subjects with type I Glanzmann thrombasthenia (PLTs lack glycoprotein IIb/IIIa complex) or congenital FcγRIII deficiency on neutrophils. The working hypothesis of the PS phenomenon is that EDTA, by chelating Ca2+ ions, changes the PLT membrane and unmasks (crypto) antigenic structures on PLT GPIIb/IIIa and PMN neutrophils, and then the IgG recognizes them forming a bridge between the two cells. Why PS patients produce these IgG (auto)antibodies and what is the mechanism of their interaction with target molecules on PLT and PMN membranes, are still unclear.

PS is clinically relevant as a possible cause of spurious thrombocytopenia. It is not associated with PLT dysfunction or hemorrhagic diathesis. When PS occurs, PLT counts are moderately reduced (from 50 to 100 × 109/L) leading to pseudothrombocytopenia or not, like in our patient.

Failure of recognizing PS as the cause of pseudothrombocytopenia can lead to unnecessary laboratory testing, delay of surgery, and needless transfusions or bone marrow aspirations. Even though automated hematology analyzers are of widespread use in clinical laboratories, they are not always reliable in reporting error flags that could instigate suspicion. However, a simple means of excluding pseudothrombocytopenia and, thus, PS in the operative setting is the simultaneous collection of blood with two anticoagulants, EDTA and citrate, and comparison of PLT counts obtained from both specimens. Furthermore, a peripheral blood smear provides definitive evidence of pseudothrombocytopenia caused by PS. Performing a blood smear from the citrate-anticoagulated blood and/or a fingertip smear will show no PLT rosetting around PMN, which is an additional confirmation of the presence of PS.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

A man with two penises: A rare case report

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Abstract

Diphallia, commonly referred to as penile duplication, is a relatively rare congenital anomaly. It affects one out of every 5.5 million live infants. The degree of penile duplication and the number of associated anomalies varies greatly, ranging from a double glans from a penis without an accompanying aberration up to total penile duplication linked with multiple anomalies. In this case, a 65-year-old man is seen with a cleft scrotum and complete bifid diphallia.

Keywords: congenital anomaly, diphallia, duplicate penis

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INTRODUCTION

Diphallia with cleft scrotum is a rare congenital anomaly that affects the male genitalia. It is distinguished by having two penises and a split that separates the scrotum into two sections. Another name for the ailment is diphallus or diphallia. Diphallia is thought to occur in 1 in 5.5 million live births. No known familial or genetic susceptibility exists. Although the precise cause of diphallia with cleft scrotum is unknown, it is thought to be connected to aberrant urogenital system development during the embryonic stage. Other anomalies such as hypospadias, epispadias, bladder exstrophy, renal agenesis, and imperforate anus may also be present in the patient.[1]

Diphallia with cleft scrotum is often identified at birth or during infancy based on a physical examination of the genitalia.[2] The condition may cause the person who has it to experience social and psychological problems as well as problems with their sex and urination. Treatment options for diphallia with a cleft scrotum can include surgery, hormone therapy, or counseling, depending on the type and severity of the abnormality.[1,3]

CASE REPORT

A 65-year-old man was diagnosed with complete bifid diphallia with a cleft scrotum alone [Figure 1]. Since birth, he claimed to have had two healthy penises, each with its own urethra and corpus cavernosum. He had never previously experienced urinary tract infections, incontinence, erectile dysfunction, or sexual problems. He was married and had a normal family and social life. He denied having been exposed to any drugs, illnesses, or trauma when his mother was pregnant. He did not have any relatives who had diphallia or any other congenital defects.

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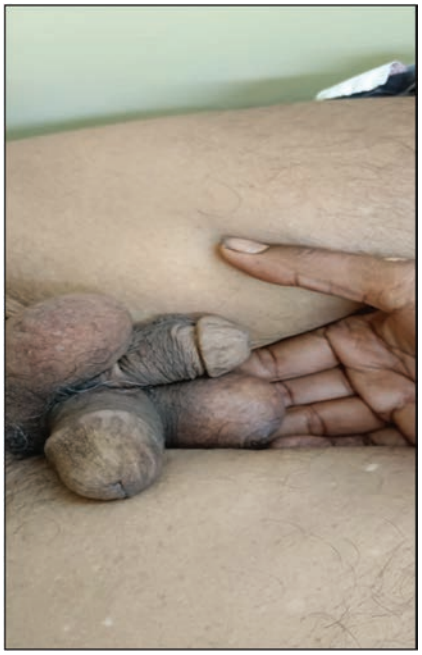

Figure 1: Double penis without any anomalies in a 60-year-old man

Upon physical examination, two perfectly formed penises, side by side in the sagittal plane, were found to be of comparable size and shape. When flaccid, each penis was roughly 3.5 cm in diameter and 7 cm long. Each penis had normal and circumcised glans. At the end of each glans was the urethral meatus. A midline raphe separated the scrotum into two sections, each of which contained a testis of average size. Hypospadias, epispadias, chordee, or phimosis were not present. The remainder of the examination of the genitalia and perineum was uneventful.

The patient received several laboratory tests, all of which were within normal ranges. These tests included a complete blood count, serum electrolytes, renal function tests, liver function tests, and urine analysis. The patient declined to have any additional imaging testing because there were no other complaints. According to further examinations, the urinary tract was not obstructed.

The patient received counseling regarding his illness and his surgical treatment options. He eschewed any surgical treatment in favor of conservative treatment. He was instructed to report any signs of urinary tract infection or malfunction and to follow up with urology frequently. In addition, a psychologist was suggested to him for guidance and assistance.

DISCUSSION AND LITERATURE REVIEW

The degree of the duplication can vary, and probable explanations including mesodermal banding failure or mesoderm encountering two urethral anlagen have been suggested. Possible presentations range from a little auxiliary penis to a complete duplicate of the urethra, glans, and corporal bodies. Most often, the orientation is parallel, and there is frequently a size discrepancy. Hypoplasia, scrotal anomalies, duplicate bladders, renal anomalies, exstrophy defects, and anatomical and cardiac anomalies are only a few of the abnormalities are often associated. This condition was categorized by Schneider as duplication of the glans only, Bifid or incomplete diphallia with a single, corpus cavernosa in each phallus, and Complete diphallia with each penis having two corpora cavernosa and one corpus spongiosum.[3] The diphallia in this case is classified as a complete diphallia following the physical examination.

Aleem's 1972 categorization, which is the most commonly used, categorizes diphallia into two groups: real diphallia and bifid phallus. Each phallus must have two corpora cavernosa and one corpus spongiosum with a urethra to be considered truly diphallia. True diphallia can be either full, with the size of both penises being similar, or partial, with one of the phalluses being smaller or juvenile but structurally identical to the bigger one.[4]

In situations with diphallia, the level of erectile function varies greatly. Most of the time, one or both penises can be erection. There have been reports of simultaneous erections and, occasionally, ejaculations in cases with real, complete diphallia that manifested at an advanced age. Even though it is yet unknown how erectile function will be following surgery, some studies have documented normal erection of partial bifid phallus and true partial diphallia.[5,6]

On the contrary, many experts agree that during the 15th week of gestation, anomalies occur during the process of migration ventrally and the union of the paired mesodermal anlagen.[7] Because the cloacal membranes in complete diphallus are longitudinally duplicated, three to four columns of primitive streak mesoderm can migrate ventrally around the two cloacal membranes to generate two genital tubercles. The extent of these cloacal membrane separations may result in anomalies such as anterior wall deficiencies, bladder exstrophy, and hindgut anomalies, and it may also be the cause of the anorectal anomalies present in the caudal duplication syndrome, which can occasionally include diphallia.[8,9]

By defining the corporal development and urethral anatomy, a thorough analysis of the external genitalia anatomy aids in the excision or restoration of the duplicate penis as well as in classifying the degree of penile duplication.[10]

The main goals of treatment are to maintain continence and erectile function while also taking into account the specific congenital defects that are present and to provide normal urine continence, urinary stream, and erection with sufficient cosmesis.[1,10,11]

CONCLUSION

Diphallia with cleft scrotum is a rare congenital anomaly that affects the male genitalia, which is distinguished by having two penises and a split that separates the scrotum into two sections. The condition is also known as diphallus or diphallia. The condition may cause the person who has it to experience social and psychological problems as well as problems with their sexual and urination. It is complete diphallia in this case, as determined by a physical examination of the genitalia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Selective angioembolization in symptomatic renal angiomyolipoma: A series of four cases along with review of literature

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Abstract

The management of renal angiomyolipoma (R-AML) should be characterized on the basis of symptoms and/or the presence of associated risk factors of hemorrhage. In total, four cases of large symptomatic R-AML were visited in our urology out-patient department within the 9-month period. They underwent selective angioembolization (SAE) and were followed up for at least 3 months. Case 1—A 40-year-old female with bilateral R-AML, largest 4 cm × 8 cm × 9 cm lesion on right kidney. Postangioembolization, she underwent a right partial nephrectomy and is in further follow-up with contrast-enhanced computed tomography of the kidney ureter bladder (KUB) region (CECT KUB). Case 2—A 36-year-old female had bilateral large R-AML associated with active bleeding and perinephric hematoma on her right side and underwent urgent SAE. Follow-up CECT KUB revealed bilateral large AML with no evidence of perinephric hematoma. Now, we are planning for a bilateral partial nephrectomy. Case 3—A 52-year-old female with symptomatic 54 × 53 mm left mid-pole R-AML. She developed postembolization syndrome and managed it conservatively. Follow-up CECT KUB revealed a marked reduction of the left R-AML lesion (1 cm × 1 cm). Case 4—A 41-year-old female with 44 mm × 40 mm exophytic upper pole right R-AML with active bleed underwent urgent SAE. Follow-up CECT KUB revealed right kidney AML lesion size reduction (27 mm × 28 mm) with no perinephric hematoma. SAE is better suited for AML with acute hemorrhage or patients with multiple comorbidities or multiple AML lesions. For large AMLs, SAE can also be used before surgery to decrease the size of tumors and the possibilities of procedural difficulty for nephron-sparing surgery.

Keywords: AML, nephron-sparing surgery, postembolization syndrome, renal angiomyolipoma, selective angioembolization

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INTRODUCTION

Renal angiomyolipoma (R-AML) is a rare benign hamartomatous tumor composed of dysmorphic blood vessels, smooth muscle elements, and mature or immature adipose tissue [1]. AMLs are believed to originate from the perivascular endothelial cells and, therefore, are also referred to as perivascular epithelioid cell tumors

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(PEComas). AML is mostly sporadic (about 80% cases) or associated with genetic syndromes, commonly tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis (LAM).[2] The prevalence of R-AML is estimated to be about 0.13% in the general population.[3] These tumors have a strong predilection for 30–50-year-old women[4]; female-to-male ratio is 4:1.[5]

The management of R-AML should be characterized on the basis of sporadic versus syndromic AML, symptoms, and/or the presence of associated risk factors of hemorrhage. Spontaneous hemorrhage can become an immediate life-threatening situation. The natural history of <4 cm size R-AMLs mostly remains asymptomatic and has a low risk for hemorrhagic complications [1]. For those R-AMLs 4 cm or larger, 50%–90% of cases are symptomatic, and 50%–60% bleed spontaneously. Such large symptomatic R-AML can be considered for treatment via selective arterial embolization (SAE), enucleation, partial, or total nephrectomy.[6]

CASE 1

A 40-year-old female patient had complained of continuous dull aching right flank pain without any radiation for 3 months. Abdominal examination revealed a firm, nontender, ballotable mass in the right lumbar region measuring approximately 12 × 10 cm, which moved with respiration. Contrast-enhanced computed tomography of the kidney ureter bladder (KUB) region (CECT KUB) showed multiple well-defined fat density lesions (size 4 cm × 8 cm × 9 cm, -50 to -80 Hounsfield unit (HU)) with the largest fatty density and contrast enhancement at the upper pole of the right kidney. Similar multiple small lesions on the left side. Radiological features suggestive of R-AML [Figure 1]. The serum creatinine was 0.9 mg/dL, and estimated glomerular filtration rate (eGFR) of 83 mL/min/1.73 m^2 was calculated using the chronic kidney disease-epidemiology collaboration method.

After thorough counseling, the shared decision was made for prophylactic SAE of the feeder vessel for the larger upper pole right renal AML lesion. The procedure was performed under local anesthesia via the right common femoral artery using a 5-Fr angiographic catheter. The major dysplastic feeder was selectively cannulated using TERUMO Progreatmicrocatheter and embolised with micro-coil MWCE-18-3.0-3 HILAL [Figure 1]. She was observed for any complications and postembolization syndrome.

Three months follow-up CECT KUB showed a decrease in size (6 cm × 5.4 cm) of the right renal AML lesion arising from mid-pole and multiple AML lesions on the left side, the largest 3 cm without much decrease in eGFR (73 mL/min/1.73 m^2) post-SAE. She underwent a right partial nephrectomy.

CASE 2

A 36-year-old female had sudden onset severe right flank pain for 2 days. Her pulse rate was 106/min and blood pressure 96/64 mm Hg. She had Hb—5.8 gm% and total leucocyte counts 11,800/cumm, serum creatinine 0.8 mg/dL with eGFR (98 mL/min/1.73 m^2). CECT KUB reported well-defined 10 cm × 6 cm exophytic right upper pole R-AML with active bleed and perinephric hematoma. Left kidney 7 cm × 9 cm AML arising from mid and lower pole noted [Figure 2A]. Two units of blood were transfused, and the patient prepared for urgent SAE.

On the table, the angiogram shows two feeder vessels arising from the right upper segmental renal artery branch

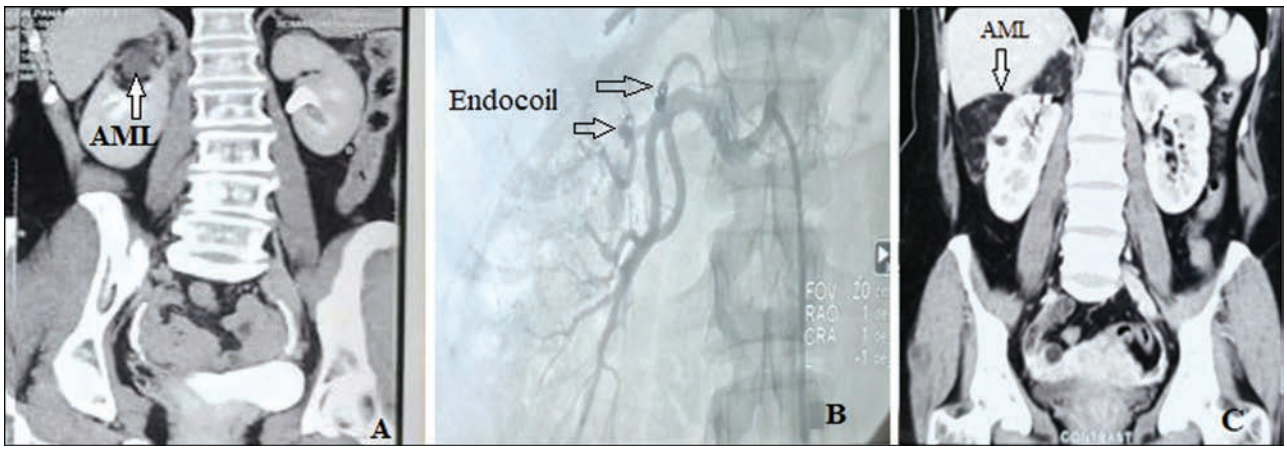

Figure 1: Case 1 CECT kidney ureter bladder coronal view shows a fat attenuated AML lesion in the right kidney. (A) Pre-embolization AML lesion, (B) angioembolization of the two feeder vessels done using micro-coil, (C) 3 months postembolization AML size decreased, the coil in the upper pole right kidney seen as an artifact

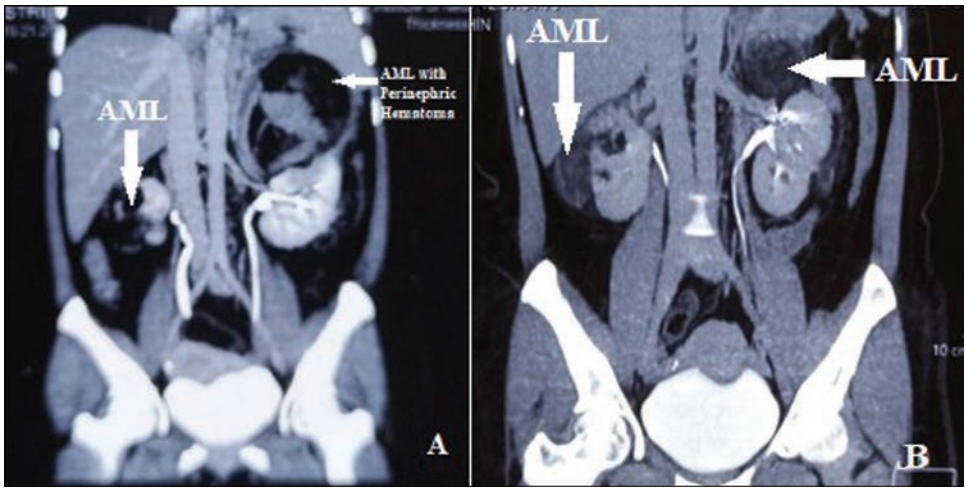

Figure 2: Case 2 (A) CECT kidney ureter bladder coronal view shows fat attenuated AML lesion in left upper pole with perinephric hematoma and right AML involving mid and lower pole. (B) Post angioembolization at 3 months, no perinephric hematoma with reduced left AML size. No significant increase in size for the right AML lesion

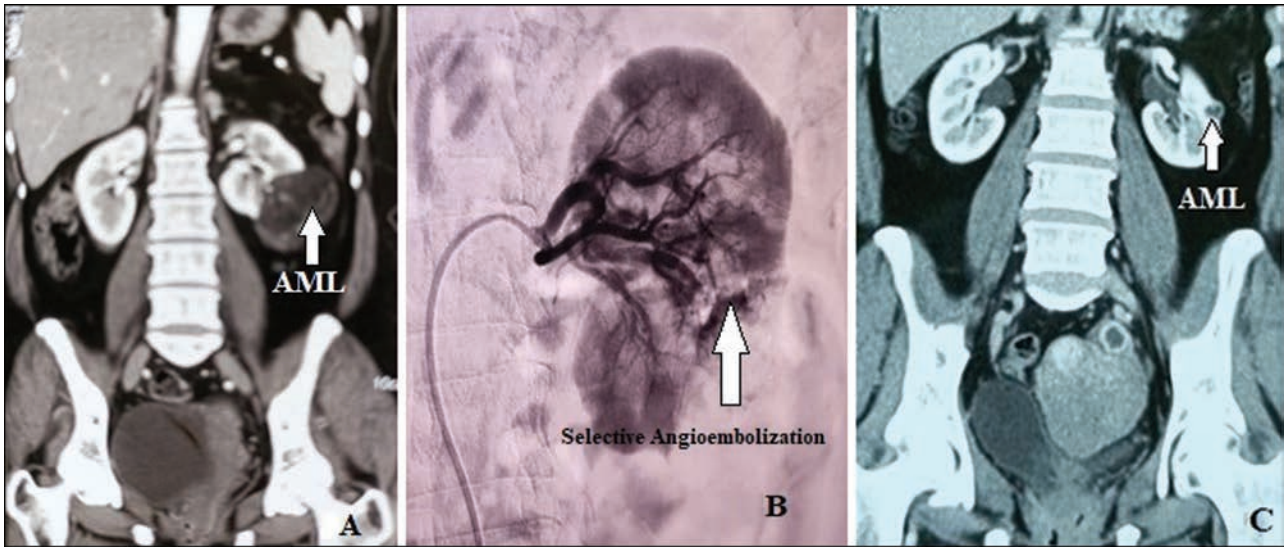

Figure 3: Case 3. (A) CECT kidney ureter bladder shows the left R-AML mid-pole. (B) Angioembolization of the feeder vessel. (C) CECT kidney ureter bladder at 3-month follow-up significantly reduced the size of AML

supplying the mass. Embolization of both feeder vessels was done by polyvinyl alcohol particle (355–500 µm) done, and 3 × 3 mm endocoil was placed at the distalmost part of the right upper polar branch for surgical localization if needed. Three-month follow-up CECT KUB revealed 7 cm × 8 cm AML of the left kidney. Right kidney AML lesion size 8 cm × 9 cm with no evidence of perinepheric hematoma [Figure 2B]. Her serum creatinine was 0.78 mg/dL with eGFR 101 mL/min/1.73 m^2. Now, we are planning for a right partial nephrectomy followed by a left partial nephrectomy.

CASE 3

A 52-year-old female with dull aching pain in her left flank for 2 months. CECT KUB reported 54 × 53 mm, HU—35 left mid-pole R-AML [Figure 3A]. Her serum creatinine was 1.05 mg/dL with an eGFR of 64 mL/min/1.73 m^2. On the table, an angiogram shows an interpolar branch arising from the upper division of the renal artery supplying the mass. Embolization by polyvinyl alcohol particle (250–350 µm) done [Figure 3B]. Postembolization patient fever on day 2 with total leucocyte counts 14,200/mm^3. This was managed conservatively. Follow-up CECT KUB revealed an exophytic 1 cm × 1 cm AML lesion in the mid-pole left kidney [Figure 3C]. Her serum creatinine was 1.1 mg/dL with eGFR 60 mL/min/1.73 m^2. Presently, she is under follow-up.

CASE 4

A 41-year-old female with a known case of right kidney upper pole AML had sudden onset pain in the abdomen

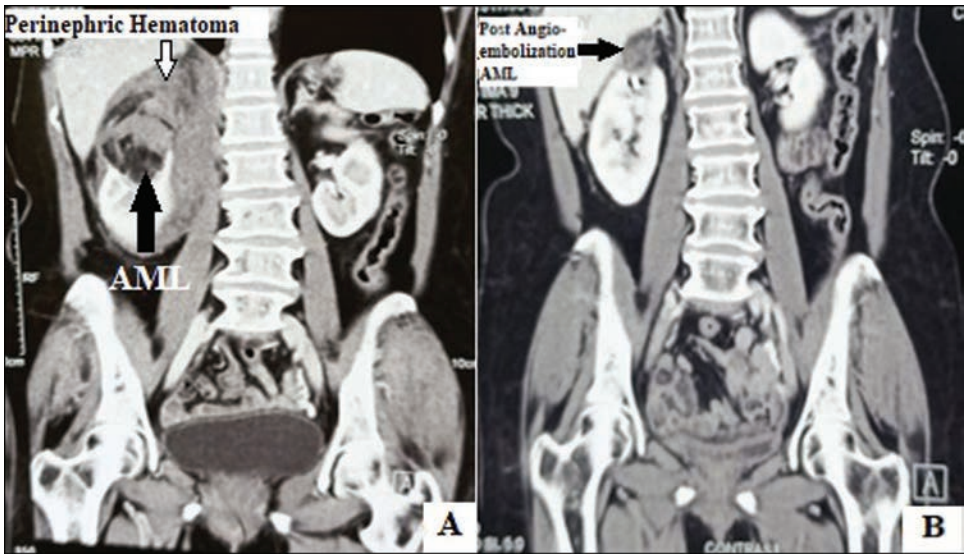

Figure 4: Case 4 (A) AML right upper pole with perinephric hematoma. (B) Post angioembolization, right kidney AML size reduced significantly with no evidence of perinephric hematoma

radiating to her back. Her hemoglobin was 10.2 mg/dL and serum creatinine 0.9 mg/dL with eGFR 82 mL/min/1.73 mm^2. On CECT abdomen, 44 mm × 40 mm exophytic upper pole AML with active bleed and large perinephric hematoma [Figure 4A]. She underwent urgent SAE. AML was supplied by two feeder vessels, and an intra-AML aneurysm was noted. Both the feeder vessels embolised with PVA (355–500 µm) and one coil (3 mm × 3 mm) placed at the distal-most part of the upper pole for future surgical localization is needed. Three months follow-up CECT KUB revealed a marked reduction in the size of the right kidney AML lesion to 27 mm × 28 mm with no perinephric hematoma [Figure 4B]. Her serum creatinine was 1 mg/dL with eGFR 73 mL/min/1.73 mm^2. Presently, she is under follow-up.

DISCUSSION

Indications for intervening R-AML include symptoms, lesion size, associated risk factors for R-AML spontaneous hemorrhage, renal function, pregnancy plans, suspicion of carcinoma in low-fat content AML, and patient's compliance.[2] Treatment options include active surveillance, surgical management, embolization, or systemic therapy (mTOR inhibitors in tuberous sclerosis). Active surveillance is an option for asymptomatic R-AML lesions without risk of bleeding. Oesterling *et al.*[6] initially proposed R-AML size 4 cm as a threshold for intervention due to their increased risk of being symptomatic. The decision on prophylactic treatment depends on the risk factors for spontaneous R-AML rupture. The important predictors of bleeding in R-AML are tumor size, growth rate,[7] women of childbearing age,[4] tuberous sclerosis, and intralesional aneurysm >5 mm.[8]

The surgical approach provides us the advantage of complete lesion resection, pathological confirmation of renal SOL, lower risk of local tumor recurrence, lower retreatment, and preservation of renal function.[9]

The advantages of SAE include minimal invasiveness of the procedure, renal preservation, and provide rapid stabilization in cases of acute hemorrhage. In AML, having multiple feeder vessels, SAE is technically challenging due to the increased risk of embolizing normal renal tissue and/or increased chance of recurrence if any feeder remains patent after the angioembolization procedure.[10] There are no specific radiologic features that strongly support the use of SAE over surgery. With large AMLs, SAE can also be used before surgery to decrease the size of tumors and the possibilities of procedural difficulty.

As per the International TSC consensus conference (2012)[11] recommendation, the first line of treatment for TSC-associated growing asymptomatic AML is mTOR inhibitors. For AML presenting with acute hemorrhage, angioembolization followed by corticosteroids is the first-line therapy. The EXIT-2 trial reported that 42% of patients with TSC or LAM and AMLs of >3 cm treated with Everolimus 10 mg daily had >50% size reduction in the tumor after 6 months of initial follow-up.[12]

Limited comparative studies between the outcome of active surveillance, nephron-sparing surgery (NSS), and SAE are available. Fernández-Pello *et al.*[13] found active surveillance was the most preferred option in 48% of the cases, followed by surgery in 31% and SAE in 17% of the cases. Spontaneous bleeding was reported in 2% of patients

who opted for active surveillance, and active treatment was undertaken in 5%. SAE reduced AML volume but required retreatment in 30% of the cases. Retreatment with SAE is mostly preferred (60% after surgery vs. 80% after SAE).

The follow-up guidelines after the initial management of AML via any modality are lacking. Most urologists follow up with patients either via ultrasonography and CECT abdomen to observe tumor growth rate or tumor recurrence.

CONCLUSION

The primary treatment options are SAE and NSS. SAE is a less invasive treatment. NSS offers a lower risk of recurrence and secondary procedure. Both appear to be safe, and the current evidence does not recommend one over the other in the average patient. However, for treating AML with acute hemorrhage or AML patients with multiple comorbidities or multiple AML lesions, SAE is better suited. With large AMLs, SAE can also be used before surgery to decrease the size of tumors and the possibilities of procedural difficulty for NSS. Follow-up with CT or ultrasonography is recommended.

Consent to participate

Patient participation consent is taken.

Consent for publication

All the authors have unanimously given consent for this article to be published in your esteemed journal (*African Journal of Urology*).

Availability of data and material

All required data are provided in the case series manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Authors' contributions

Swadeep Kumar Srivastava: Design, materials, data collection and processing, analysis and interpretation, writing; Krishnendu Maiti: Conception, design, supervision, data collection and processing, analysis and interpretation, literature review, writing, critical review; Soumya Mondal: Design, analysis, and interpretation.

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Case Series

Parameatal cyst: A case series with review of literatures

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Abstract

Parameatal cyst of the external urinary meatus is a rare entity. In most of the cases, the patients are asymptomatic, and they are presented due to poor cosmesis. Complete surgical excision gives the best result in terms of recurrence. Here, we present a series of four cases of such cysts. The relevant literatures are reviewed.

Keywords: Cyst, parameatal, penile

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INTRODUCTION

Parameatal cyst is a rare entity in both sexes, and near about 50 cases have been reported in the literature till now.[1,2,3] The cyst usually occurs in one side of the urethra, and sometimes they may be bilateral.[4] Usually, these cysts are asymptomatic, and the patients present due to poor cosmesis, difficulty to void, or pain during intercourse.

CASE REPORTS

Case No. 1

A 25-year-old unmarried man presented with a small cystic lesion on the external urinary meatus of the size of a pea, but slowly increased in size by 1 year. There was no history of trauma or swelling. His only complaint was poor cosmesis, and he presented to us before marriage with an apprehension of sexual difficulty. Upon clinical examination, there was a 1 cm diameter nontender cystic swelling on the left lip of the external meatus [Figure 1]. Under local anesthesia, the cyst was excised, and the margins were sutured. The histopathological examination suggested the cyst wall was lined by transitional epithelium [Figure 2A]. There were no recurrences till 3 years of follow-up.

Case No. 2

A 36-year-old married male presented with bilateral cystic lesions on the external urethral meatus for 1 year. He presented to us due to difficulty in intercourse with a fear of rupture of the cysts during intercourse. He did not have any voiding difficulty or any other symptoms. On examination, there were two nontender cysts in both the lips of the external urethral meatus [Figure 3]. The cysts were excised under spinal anesthesia, and the margins were sutured, placing a catheter. The wound healed in 5 days, and the catheter was removed. Histopathology suggested the cyst wall was lined by nonkeratinized stratified squamous epithelial lining of the penile meatus [Figure 2B]. Till 1 year of follow-up, there was no recurrence.

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Case No. 3

A 6-year-old boy presented to us with a cystic swelling at the tip of the penis with a deviation of the urinary stream toward the left side. On examination, there was a nontender cyst of 0.5 × 0.5 cm on the right lip of the external urinary meatus. The cyst was excised under anesthesia, and the margins were sutured. Histopathological examination suggested the cyst wall was lined by transitional epithelium without any atypia [Figure 2C]. No recurrence was found during 3 years of follow-up.

Case No. 4

A 36-year-old married man presented with a small cystic swelling in the lower part of the external urinary meatus for the last 6 months. Apart from poor cosmesis, he did not have any other symptoms. On examination, here was a nontender cystic swelling of 1 cm × 1 cm size arising from the lower part of the external urinary meatus [Figure 4]. Under local anesthesia, the cyst was excised, and the margins were repaired. Histopathological examination suggested the cyst wall was lined by transitional epithelium [Figure 2D]. There was no recurrence till 6 months of follow-up.

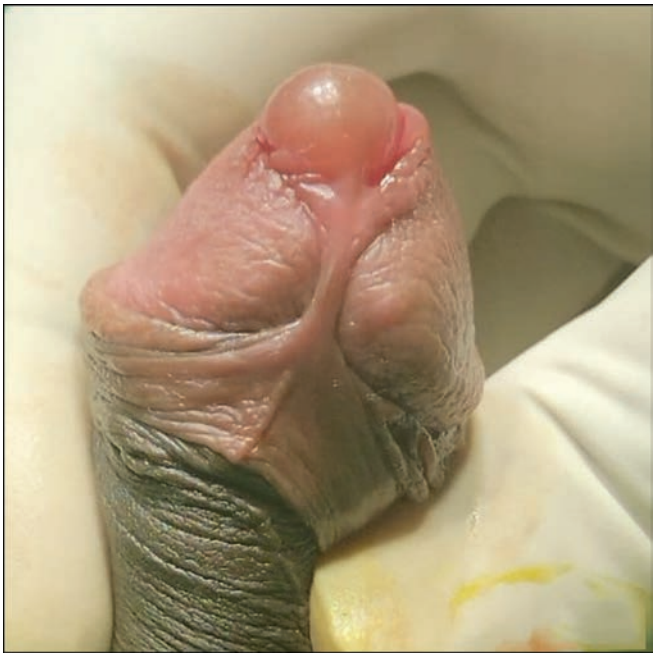

Figure 1: Parameatal cyst arising from the left side of the external urinary meatus

DISCUSSION

The parameatal cyst was first described by Thompson and Latin in 1956.[4] The pathogenesis of these cysts is not been cleared till now. Some say it develops due to delamination or separation of the foreskin from the glans.[4] Some are of the opinion that it occurs due to occlusion of the paraurethral duct.[5,6,7]

The cysts are usually asymptomatic. It is rare that they cause any urinary obstruction. Only one case of acute urinary obstruction was reported in a female patient.[8] They may present with bleeding due to rupture. Sometimes, they may present due to sexual difficulty as in our case no. 2 or splaying of the urinary

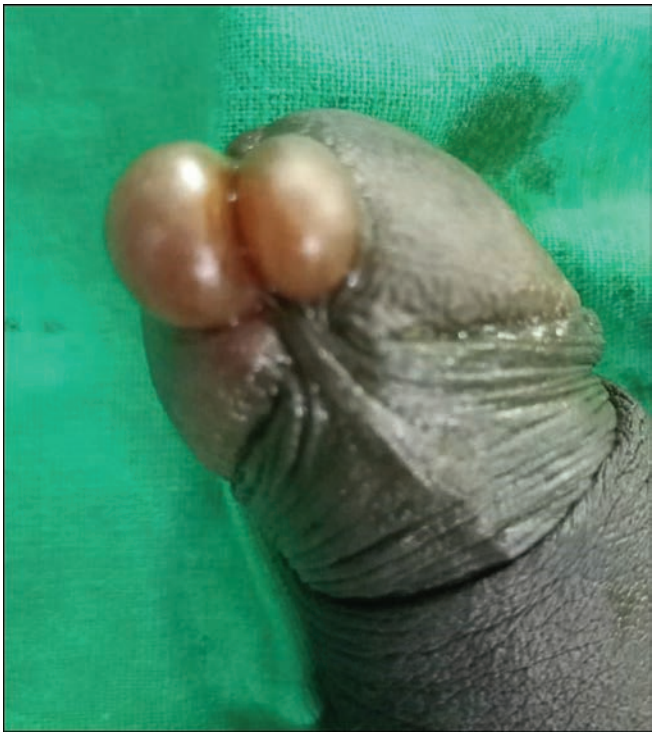

Figure 3: Parameatal cyst arising from the both sides of external urinary meatus

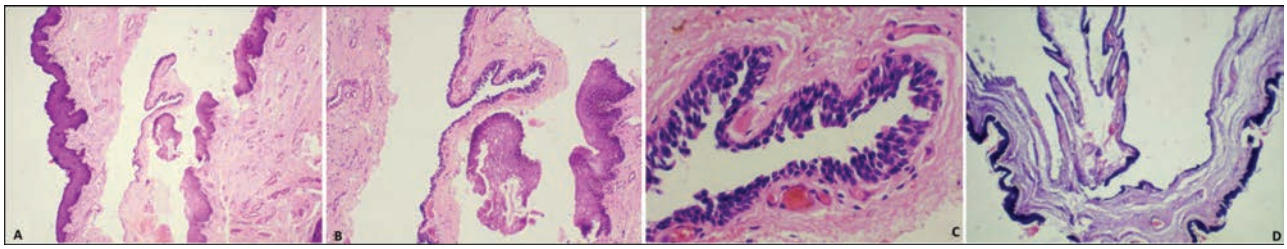

Figure 2: (A) Cyst wall lined by transitional epithelium (H&E ×40). (B) Cyst wall and adjacent nonkeratinised stratified squamous epithelium of penile meatus (H&E ×100). (C) Lining epithelium of the cyst wall, transitional epithelium without any atypia (H7E ×400). (D) Cyst wall lined by transitional epithelium (H&E ×400)

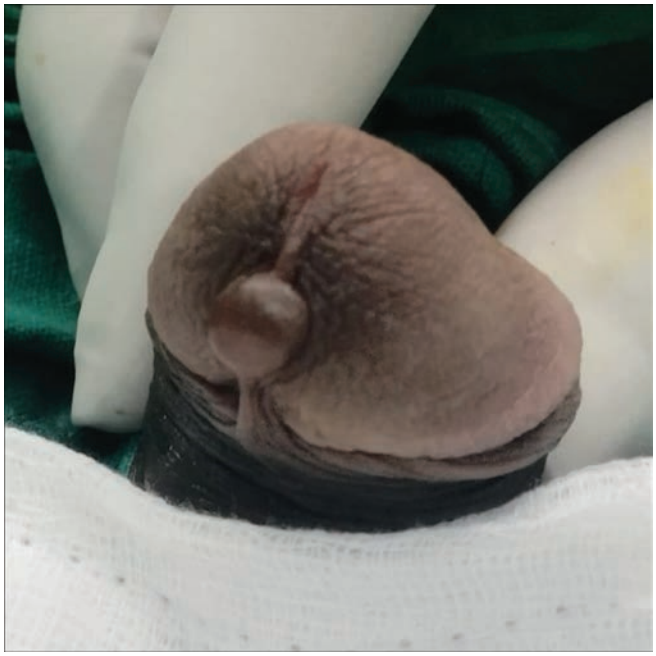

Figure 4: Parameatal cyst arising from the lower part of the external urinary meatus

stream, as in our case no 3. The differential diagnoses are epidermoid cyst, pilosebaceous cyst, or fibroepithelial polyp.

Surgical excision is the treatment of choice.[1–4] Marsupialization results in unsatisfactory cosmesis. Aspiration of cyst invariably results in recurrence.[9] After complete surgical excision, recurrence is unknown.[9]

CONCLUSION

Parameatal cysts are benign and usually asymptomatic lesions. Patients usually present for poor cosmesis or splaying of the urinary stream. Surgical excision is the treatment of choice.

Acknowledgement

None.

Ethical clearance

Necessary permission was obtained from the Ethical Clearance Committee of IPGME&R.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Clinical Image

Van Wyk–Grumbach syndrome

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This 7-year-old female, born out of non-consanguineous marriage, normal vaginal delivery, first in birth order without any history of prolonged perinatal complications presented with short stature, progressive enlargement of breasts, and galactorrhoea. Developmental milestones were achieved as per age, but her scholastic performance is below average. Menarche was attained at 5 years. Despite pubertal precocity, she had no pubic or axillary hair.

On examination, height was 112 cm (less than third percentile) and weight 27.3 kg (50th–75th percentile). She had B4 breasts with no pubic or axillary hair. She had dry scaly skin.

Thyroid function tests showed primary hypothyroidism, fT4 0.23 ng/dL (0.8–2.0), thyroid stimulating hormone (TSH) > 75 mIU/mL (0.4–4.4), anti-thyroid peroxidase antibody > 100 IU/mL (<35). Serum insulin like growth factor-1 was low and serum prolactin was high (88 ng/mL). Serum leuteinizing Hormone was prepubertal with high follicle stimulating hormone (FSH). Bone age was 5 years. MRI showed diffuse pituitary enlargement [Figure 1A]. USG pelvis revealed large multicystic ovaries (right ovary volume: 66.82 mL, left ovary volume: 49.65 mL) [Figure 1B].

This is a case of Van Wyk–Grumbach syndrome, a combination of short stature, precocious puberty with multicystic ovaries, and pituitary hyperplasia due to untreated primary hypothyroidism. Pituitary hyperplasia occurs due to feedback hyperplasia by stimulation with thyrotropin releasing hormone. At the level of ovary, TSH stimulates FSH receptors due to "specificity spillover" and causes multicystic changes.[1,2] High prolactin may increase the sensitivity of ovaries to circulating gonadotropins.[3] Levothyroxine replacement results in dramatic improvement with shrinkage of hyperplastic pituitary and ovarian volume.[4]

Precocious puberty with pituitary hyperplasia in the presence of short stature and delayed bone age gives clues towards Van Wyk–Grumbach syndrome, which may avoid unnecessary surgical misadventures.

Disclosure

The authors have nothing to disclose

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. The patient has given his consent for images and other clinical information to be reported

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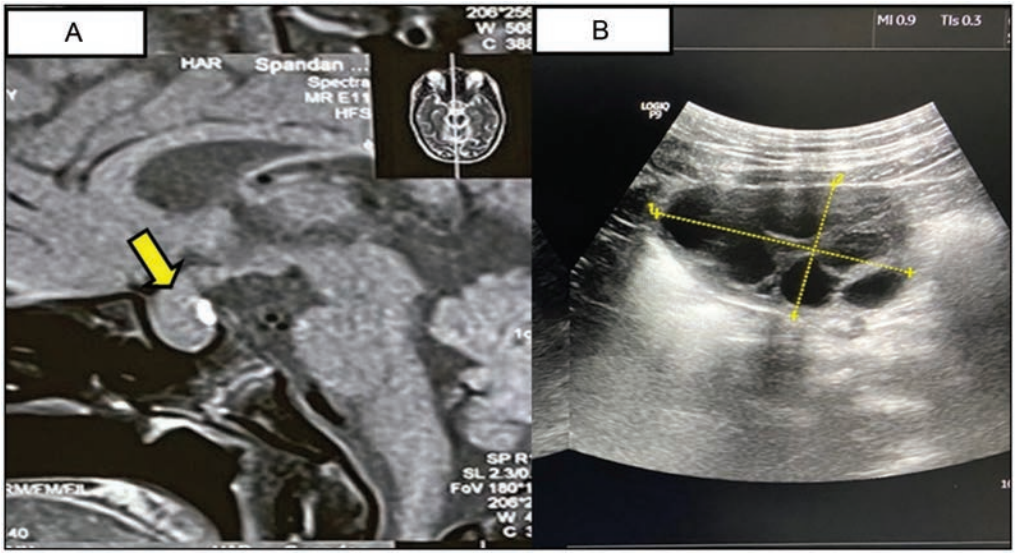

Figure 1: (A) T1 weighted MRI pituitary showing diffusely enlarged pituitary due to thyrolactotroph hyperplasia. (B) USG pelvis showing large multicystic right ovary (volume: 66.82 mL)

in the journal. The patient understands that names and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There were no conflicts of interest.

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Letter to the Editor

Role of digital behavior change interventions in combating chronic diseases

Dear Editor,

Information and communication technology has revolutionized the healthcare industry tremendously. According to official Telecom Statistics published by India in 2021–2022, the number of Internet subscribers increased to 834.29 million by the end of September 2021.[1] Due to its great usability and capacity to meet people's demands in various contexts thanks to interactivity, quick information access, and practicality, smartphones and tablets have gained popularity. It is anticipated that using mobile health (mHealth) technology will result in health behavior change. In India, one in four individuals is at risk of dying from chronic illnesses, which include obesity, diabetes, and hypertension.[2] People who reside in the rural parts of India accessing health care services is challenging due to transportation issues, hence adopting the mHealth services would be an alternative. In many countries, the cost of managing these chronic diseases already accounts for a considerable proportion of all healthcare expenditures. A recent systematic review from America has reported that the high mortality rate linked to chronic diseases is correlated with a more sedentary lifestyle, and non-adherence to treatment plans, which has also been linked to many patient-related factors like forgetfulness, psycho-social stress, anxieties, and low motivation.[3]

Behavior change-based interventions using digital technology can be incorporated to improve the care management of patients with chronic diseases. Internet-based interventions to promote health behavior change can be employed by telemedicine, an e-platform system such as educational modules, and wearable digital activity monitor which track physical activity, including daily step counts and active minutes for individuals with sedentary lifestyles can be used. Alarm-triggered reminders make it easier for people to embrace and integrate both the drug and treatment adherence, thus it can reduce the risk of relapse and symptom severity. Digital behavior change interventions (DBCIs) assist and encourage behavior changes that will improve and promote health through primary or secondary prevention and management of health conditions. Additionally, this technology promotes behavioral strategies by sending out health-related information, keeping track of goals, and encouraging behavioral change to enhance people's health conditions.

Once a substantial segment of the population adopts digital interventions for lifestyle adjustments, favorable transformations in health-related behavior will lead to lower healthcare utilization and eventually a significant decrease in healthcare expenditure. At the same time, it is crucial to take into account any potential difficulties when employing technology in a group of older persons given the rise of technology-based treatments to encourage healthy behaviors. Working with this demographic has several difficulties, including low technology efficacy, complicated technology use, and physical constraints.[4]

The need for thorough application development is essential, with proper scientific and technical foundations, and evaluation of the effectiveness of these behavioral strategies involving populations with difficulties in accessing the internet and information technology as well as involving the elderly population is vital. Business and technology leaders and medical professionals can collaborate to offer more substantial digital transformations, meaningful disruptions, and valuable experiences to aid individuals on the next level by having a deeper grasp of healthcare demands. This strategy can boost technology adoption in the healthcare sector by encouraging small adjustments that build up to considerable improvement. Digital behavioral-based interventions and proper care management can alleviate patient suffering, improve prognostic outcomes, and improve the well-being of patients by adding the vital missing layer of support needed to incorporate behavior change.

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There are no conflicts of interest.

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Obituary

Obituary Prof. Dilip Kumar Pal

(28 DECEMBER 1962– 5 JANUARY 2024)

Prof. Dilip Kumar Pal, a persona exuding the confidence of a loving teacher, an able administrator, and a great mentor, fulfilling many roles in the Institute of Postgraduate Medical Education & Research (IPGME&R)-SSKM Hospital, Calcutta, West Bengal, India, and West Bengal University of Health Sciences, Calcutta, West Bengal, India left for his heavenly abode after a massive myocardial infarction on January 5, 2024.

From a humble beginning in rural Bankura, a district in the interior areas of West Bengal, to reaching the heights as a Urologist holding the president post of the East Zone Urological Society of India, the Dean of the West Bengal University of Health Sciences and a member of the West Bengal Medical Council, his journey is an inspiring story of struggle and fight against all odds and determination to reach unchartered shores.

After schooling in Bankura, he completed his MBBS from North Bengal Medical College in 1988 and followed it with an MS (General Surgery) from Shyam Shah Medical College, Rewa, Madhya Pradesh, India, in 1992. He joined government service soon after and was posted at North Bengal Medical College. He completed his MCh (Urology) from the Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India, in 1999 and moved to the Department of Urology in State Medical Education Service, the following year.

He has been in government service since 1993 and served in various medical colleges of the state like North Bengal Medical College, Bankura Sammilani Medical College, and Medical College Kolkata for more than 20 years in various teaching capacities. He started working in IPGME&R, Kolkata as Head of the Department of Urology on January 1, 2014.

He played an instrumental role in taking the Urology department of IPGME&R -SSKM Hospital to new heights. Turning it from a 45- to 110-bed department in a separate Uro-Nephro Institute has one of the highest student and resident strengths in the country. It was his dream to see IPGME&R Urology as an Institute of repute in the country. Toward this goal, with great support from the College and Hospital administration, he took the necessary initiatives to muster necessary clearance to ensure the Uro-Nephro Institute with a separate 10-storeyed dedicated building and 110 beds each for Urology and Nephrology. Presently, the Urology Department of IPGME&R, nurtured under his guidance, is a premiere Urology institute in Eastern India offering a standard of care treatment to urological patients. The Uro-Nephro Institute at IPGME&R holds a prestigious position in the national perspective.

As a Urologist, he was a thorough clinician and possessed great surgical acumen. He was a teacher par excellence and guided over seventy MCh residents during his tenure at IPGME&R-SSKM hospital. He guided more than 45 Postdoctoral and Postgraduate thesis works and presented 104 papers at various zonal, national, and international conferences.

He was a dedicated academician and an avid researcher. He published more than 350 articles in various national and international peer-reviewed journals. For the last decade, Prof. Pal has been working to establish the association between arsenic toxicity and urinary bladder cancer. His group studied the arsenic level in bladder tumors of patients from an exposed population and established an association with the progression, recurrence, and prognosis of the disease.[1,2] They developed a methodology of immune-cytochemical detection of mini-chromosome-maintenance-protein-2 as a potential urinary-based marker of bladder cancer.[3] At the molecular level, the group led by him found the association of *BRCA1* and *BRCA2* genes and divergent

molecular profiles of the *PIK3CA* gene in arsenic-induced urinary bladder carcinoma.[4,5]

They also studied the importance of the LIMD1–VHL– HIF1α (LIM domains containing protein1-Von Hippel-Lindau-Hypoxia inducible factor-1α) pathway in development of bladder carcinoma in association with arsenic prevalence, and showed a high nuclear expression of HIF1α, synergizing with inactivation of LIMD1 and VHL that portray worst prognosis among the bladder cancer patients in association with arsenic prevalence.[6] Their research on integrative genomics and pathway analysis; identified prevalent FA–BRCA pathway alterations in arsenic-associated urinary bladder carcinoma. It was evidenced that, chronic arsenic accumulation in cancer tissues hampers the FA–BRCA (Fanconi Anemia/Breast Cancer Gene) pathway.[7] All these findings have huge future potential and prospect for the development of early diagnostic and prognostic tools and also toward the development of targeted therapy for bladder Carcinoma. For necessary echological intervention, they developed methodology of spatial mapping and modeling of arsenic contamination of groundwater and risk assessment through geospatial interpolation technique.[8]

PROF. DILIP KR. PAL AND ANNALS OF MEDICAL SCIENCE & RESEARCH

IPGME&R, the erstwhile Presidency General Hospital is the oldest general hospital in India (1707) and remains to be one of the premier healthcare and academic institutes of the country for the practice and research in modern medicine.

The institute has a glorious record of fundamental research in various fields of medicine. It was from here that Edward Hare, DD Cunningham, TR Lewis, and Ronald Martin put their mark on medical treatment and research.[9] This hospital had hosted the works of the epoch-making discovery of the "Cycle of Malarial Parasite" by the first Nobel laureate from India (1902), Sir Ronald Ross.

In the year 2020, Prof. Pal was assigned with the duty of Editor-in-Chief by the IPGME&R Faculty Council to start an academic journal, in the name and style of *Annals of Medical Science & Research* (AMSR). The institute has catered to the health needs of a very large proportion of the world population over the years, and it has been always felt the need for scientific data harvesting in this part of the world. Thus, AMSR saw the light of the day in January 2022 as a multidisciplinary open access peer reviewed journal. In the introductory editorial of the first issue of AMSR, Prof. Pal wrote, ".... India being the unique melting pot holds a fifth of the world's population, which has been churned through the ages of migrations resulting in a multiethnic, multiracial diaspora spread across its extreme geographical and cultural diversities. Apart from being an anthropological marvel, it offers a unique challenge and scope to the clinicians and scientists to study disease processes with multitudes of variations in its agent, host, and environmental factors that need not match the existing western texts. Thus, a systematic documentation of the health records, disease patterns, and health solutions available across the diverse strata of this country can not only contribute but also significantly influence and enrich the world of medical literature. The illustrious history of this organization acts as a motivation for us to excel, and it is befitting that IPGME&R would lead the endeavor, as has always been its legacy."[9]

He remained the inspiration and father figure on the editorial board, and in a short period, the journal gained tremendous acclamation and popularity among medical academics with his untiring efforts. He was a tough taskmaster and a disciplinarian and instilled the cult of excellence and sincerity in the journal activities.

On the organizational front, he was a council member of the Urological Society of India in 2016–2018, and the president of the Urological Society of India (East Zone) in the year 2018–2019.

He held the post of Dean, at the Faculty of Modern Medicine, West Bengal University of Health Sciences, and made widespread reforms to dissertation protocol and examinations. He was also an elected member of the West Bengal Medical Council.

His untimely and sudden demise has left a huge void, which is difficult to fill.

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Conflicts of interest
There are no conflicts of interest.

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