World Journal of Experimental Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Exp Med 2025 September 20; 15(3): 107323

DOI: 10.5493/wjem.v15.i3.107323

ISSN 2220-315x (online)

ORIGINAL ARTICLE

Observational Study

Safety and efficacy of autologous bone marrow aspirate concentrate injection for idiopathic male infertility: A comparative study

Ravi Velamoor Rangarajan, Avinash Gandi Devadas, Dhossaradhan Jayakumar Padmanapan, Naveen Jeyaraman, Swaminathan Ramasubramanian, Arulkumar Nallakumarasamy, Sathish Muthu, Madhan Jeyaraman

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade C

P-Reviewer: Zhang H

Received: March 21, 2025
Revised: March 29, 2025
Accepted: April 21, 2025
Published online: September 20, 2025
Processing time: 145 Days and 3.1 Hours

Ravi Velamoor Rangarajan, Avinash Gandi Devadas, Dhossaradhan Jayakumar Padmanapan, Naveen Jeyaraman, Swaminathan Ramasubramanian, Arulkumar Nallakumarasamy, Sathish Muthu, Madhan Jeyaraman, Department of Regenerative Medicine, Mother Cell Regenerative Centre, Tiruchirappalli 620017, Tamil Nadu, India

Corresponding author: Madhan Jeyaraman, MS, PhD, Assistant Professor, Research Associate, Department of Regenerative Medicine, Mother Cell Regenerative Centre, Vayalur, Tiruchirappalli 620017, Tamil Nadu, India. madhanjeyaraman@gmail.com

Abstract

BACKGROUND

Although limited clinical evidence exists, such as case reports of azoospermia treatment in humans using bone marrow aspirate concentrate (BMAC) injection, these findings provide a compelling foundation for exploring mesenchymal stem cell therapy in male infertility.

AIM

To evaluate the safety and efficacy of autologous BMAC injection into human testis for men with severe oligospermia or azoospermia over the existing standard of care pharmacotherapy and lifestyle modifications.

METHODS

We included patients diagnosed with male infertility of the age group between 35–45 years in this trial comparing BMAC injection therapy with pharmacotherapy and lifestyle modifications over a 6-month follow-up period. Semen analysis was used to evaluate the efficacy of the interventions analyzed.

RESULTS

We enrolled 30 patients in the trial with 10 patients in each arm of the trial. Compared to the baseline, neither the BMAC group (P = 0.139) or pharmacotherapy group (P = 0.056) nor the lifestyle modification group (P = 0.112) demonstrated a statistically significant increase in sperm count at 6 months. However, the BMAC group demonstrated a significant increase in sperm count (mean 19.2 million; P = 0.001) compared to the pharmacotherapy group (mean 3.5 million) and lifestyle modification group (mean 2.2 million) at 6 months.

Significant improvement was noted in the motility grade ($P < 0.001$) only in the BMAC group while no changes were noted in the other groups.

CONCLUSION

This trial highlights the potential of autologous BMAC as a promising therapeutic option for male infertility. Despite the absence of significant changes within individual treatment arms, BMAC therapy demonstrated superior efficacy in improving both sperm count and motility compared to standard pharmacotherapy and lifestyle modifications. These findings underscore the potential role of regenerative medicine in addressing severe oligospermia and azoospermia, warranting further research to solidify its clinical applicability.

Key Words: Bone marrow aspirate concentrate; Male infertility; Sperm count; Motility; Regenerative medicine

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This trial evaluated the safety and efficacy of autologous bone marrow aspirate concentrate (BMAC) therapy for male infertility in men aged 35–45 with severe oligospermia or azoospermia. Over six months, BMAC therapy showed a significant increase in sperm count and motility compared to pharmacotherapy and lifestyle modifications. These results highlight BMAC's potential as a regenerative medicine option for male infertility, warranting further research for clinical application.

Citation: Rangarajan RV, Devadas AG, Padmanapan DJ, Jeyaraman N, Ramasubramanian S, Nallakumarasamy A, Muthu S, Jeyaraman M. Safety and efficacy of autologous bone marrow aspirate concentrate injection for idiopathic male infertility: A comparative study. *World J Exp Med* 2025; 15(3): 107323

URL: https://www.wjgnet.com/2220-315x/full/v15/i3/107323.htm

DOI: https://dx.doi.org/10.5493/wjem.v15.i3.107323

INTRODUCTION

Infertility is growing at an alarming pace in India and especially in metros, says a recent report from the International Institute of Population Sciences[1]. Between 15-20 million Indian couples are suffering from infertility every year[2,3]. For the fertility process to proceed smoothly, both the man and the woman should be healthy and normal. Although many people still think of infertility as a "woman's problem", up to half of all cases of infertility involve problems with the man. About 20%-30% of the time, a man's low fertility is the main obstacle to conception[4].

Male infertility refers to a male's inability to cause pregnancy in a fertile female. In humans, it accounts for 40%-50% of infertility[4]. Unexplained infertility where the etiology and molecular mechanism are not identifiable despite advanced diagnostic techniques is called idiopathic male infertility[5,6]. Male infertility is mainly due to the deficiencies noted in the semen quality and quantity. Hence semen analysis is used as a surrogate measure of male fertility[7,8]. Male germ cells are derived from a founder population of primordial germ cells (PGCs) that are set aside early in embryogenesis[9]. After birth, PGCs differentiate to spermatogonial stem cells (SSCs) in the male which are responsible for maintaining spermatogenesis throughout life by continuous production of daughter cells that differentiate into spermatozoa[10-12]. Causes of male infertility are more attributed to sperm dysfunctions in terms of their number, morphology, and motility. Erectile dysfunction is another emerging cause of male infertility[13,14].

The use of mesenchymal stem cells (MSCs) has emerged as a promising therapeutic approach for azoospermia, supported by extensive animal studies[15-18]. Bone marrow-derived MSCs (BM-MSCs)[19] and adipose tissue-derived MSCs[20] have shown potential in restoring spermatogenesis in azoospermic rodent models, particularly following busulfan-induced azoospermia. Transplantation of MSCs into rete-testes led to morphological normalization and spermatogenesis, with subsequent fertility recovery in some cases[21-23]. Human umbilical cord MSCs have similarly demonstrated the ability to differentiate into germ cells in seminiferous tubules, with promising results in both immunodeficient and immunocompetent mice[24].

The therapeutic effects of MSCs are attributed to their multi-faceted mechanisms, including trans-differentiation into germ cells, secretion of paracrine factors that recruit and activate resident germinal stem cells, and fusion with local cells in the testicular microenvironment[25-27]. Furthermore, Sertoli cells enhance MSC survival and support germ cell differentiation, owing to their immune tolerance properties[28,29]. MSCs' hypoimmunogenicity and immunomodulatory capacity make them suitable for allogenic transplantation, with additional benefits seen in mitigating toxic effects, such as lead-induced gonadal damage[30]. Histomorphometric analyses have also revealed structural changes in seminiferous tubules post-MSC therapy, suggesting a role for intratubular hydrostatic pressure in spermatogenesis recovery[31,32]. While MSCs derived from bone marrow, adipose tissue, and umbilical cord have demonstrated efficacy, the precise mechanisms of action remain incompletely understood, warranting further investigation.

Although limited clinical evidence exists, such as case reports of azoospermia treatment in humans using bone marrow aspirate concentrate (BMAC) injection, these findings provide a compelling foundation for exploring MSC therapy in male infertility. This study seeks to build on existing research and evaluate the potential of BMAC as an alternative regenerative treatment for azoospermia and compare its efficacy with the standard of care pharmacotherapy and lifestyle modifications.

MATERIALS AND METHODS

The comparative study was conducted in Mothercell Regenerative Centre at Maruti Hospital, Trichy, Tamil Nadu. The protocol was approved by the Plasmaart Resto Ethics Committee, Tiruchirappalli with No. PR22RVS012 dated 22.10.2022. All the procedures were carried out according to the local and national regulatory guidelines. This study was performed in full accordance with the World Medical Association Declaration of Helsinki. Before enrolling patients in the study, written informed consent was obtained after explaining the nature of the study.

Diagnosis criteria

Based on the European Association of Urology guidelines on male infertility and the World Health Organization (WHO) manual for the investigation, diagnosis, and management of the infertile male the following inclusion and exclusion criteria were framed[33].

Men with idiopathic severe oligospermia defined as less than one million sperm per ml, or men with azoospermia, men between 25-50 years of age, normal serum levels of gonadotropins, testosterone and prolactin, and absence of infectious genital disease and anatomical abnormalities of the genital tract were included in the study. Men with previous surgery in testis, those with major medical problems such as malignancy, hepatitis, *etc.*, those taking drugs like antimetabolite, anti-inflammatory, and steroid medications, and congenital defects in the external genitalia were excluded from the study.

Baseline investigation

Complete baseline investigation and biochemical tests like complete blood counts, erythrocyte sedimentation rate, blood sugar, renal function tests, liver function tests, serum levels of gonadotropins, testosterone, prolactin, follicle-stimulating hormone, luteinizing hormone, antibodies levels for chlamydia, anti-sperm antibodies were carried out. Conditions such as varicocele were ruled out. We also carried out karyotyping and semen examination as a part of screening examinations. Patients with infertility persisting for more than 2 years were examined twice before enrolment in the study.

Study groups

Once considered eligible the patients are randomized into one of the three study groups namely: (1) BMAC injection therapy; (2) Pharmacotherapy; and (3) Lifestyle modifications. The randomization process was conducted using a computer-generated sequence to ensure allocation concealment and minimize selection bias. This sequence was generated prior to participant enrolment, which provided equal allocation probabilities among the three treatment arms. However, considering the nature of the interventions no blinding could be established among the treatment arms.

BMAC injection therapy: We have based our study on the Jordan Clinical Trial[9]. Patients were thoroughly assessed for spinal anaesthesia and the physician's opinion for bone marrow aspiration was obtained. Under strict aseptic conditions orthopaedic surgeon aspirated bone marrow from the iliac crest. Total 60 mL of bone marrow aspirated with 8 mL of acid citrate dextrose. From this 60 mL, 6 mL of concentrated BMAC was prepared using the Sepax(R)System (BioSafe America Inc., Texas, United States)[10]. Once the BMAC was ready, it was injected into the seminiferous tubules at the lobuli of the testis percutaneously. After one injection the patient is observed with follow-up visits every month for 6 months. Semen analysis was performed according to WHO guidelines and included parameters such as sperm count, and motility[11] at the end of 6 months and compared to the baseline values.

Pharmacotherapy: Patients assigned to this group received capsules containing L-carnitine, L-arginine, zinc, vitamin E, glutathione, selenium, co-enzyme Q10, and folic acid, in required combinations for 6 months. Hormone replacement therapy was also instituted for patients with hormone deficiency detected by blood investigations. Patients were observed with follow-up visits every month for 6 months. Semen analysis was performed at 6 months and compared to the baseline values.

Lifestyle modifications: Patients assigned to this group received lifestyle modification advice like avoiding smoking, consuming alcohol and tobacco products, and appropriate treatment for lifestyle diseases like diabetes, hypertension, and obesity. Regular exercises and calorie-conscious high protein micronutrient-rich food with adequate anti-oxidants were recommended. Patients were observed with follow-up visits every month for 6 months. Semen analysis was performed at 6 months and compared to the baseline values.

Semen analysis

The study adhered to the WHO standards for semen analysis, as outlined in the latest edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen, to ensure reproducibility and standardization of results. Participants were instructed to abstain from sexual activity for a period of 2–7 days prior to sample collection. Semen

samples were obtained *via* masturbation, directly into sterile, wide-mouthed containers that were free from any spermicidal substances. Participants collecting samples outside the laboratory were instructed to maintain the sample at body temperature (approximately 37 °C) and deliver it to the laboratory within one hour of collection. The time of sample collection, as well as any deviations from standard protocol (*e.g.*, spillage or delayed delivery), was recorded. All samples were allowed to liquefy at room temperature for a maximum of 30 minutes. Any deviations were noted. Semen volume was measured using a graduated pipette. The concentration of spermatozoa was assessed using a hemocytometer. Sperm motility was categorized according to WHO standards: (1) Normal progressive motility; (2) Slow progressive motility; (3) Non-progressive motility; and (4) Immotility. Laboratory equipment, including pipettes and microscopes, was regularly calibrated to maintain accuracy. Confidentiality was maintained by anonymizing samples and data records.

Complications

We observed the patients for expected complications from the BMAC therapy such as donor site pain, and swelling. Following the intervention, we also looked for testicular pain, swelling, inflammation, and any other discomfort noticed by the patients.

Statistical analysis

All statistical analyses were conducted using Stata 17 software. The primary objective was to compare quantitative outcomes in semen analysis, including both nominal and continuous variables, across three groups at baseline and 6 months follow-up. Continuous variables were expressed as mean ± SD for normally distributed data, or median with interquartile range for skewed data. The normality of the data was assessed using the Shapiro-Wilk test. Continuous data were analyzed using a mixed analysis of variance model, which incorporated group (three levels) and time point (two levels) as fixed factors to determine main effects and interaction effects. If the assumption of normality was violated, appropriate transformations were applied. Post hoc pairwise comparisons were conducted using the Bonferroni correction to adjust for multiple testing. A paired *t*-test was used to evaluate the effect of intervention compared to the baseline.

Nominal variables were presented as frequencies and percentages. Group-wise differences were assessed using the χ^2 test or Fisher's exact test where appropriate. Changes over time were evaluated using Cochran's Q test for paired nominal data, and between-group differences in change were further examined using McNemar's test for post hoc analysis. Effect sizes were calculated for both continuous and nominal outcomes to assess the magnitude of differences. Statistical significance was set at a P value < 0.05 for all analyses. Missing data were handled using multiple imputation techniques to align to treat [intention-to-treat (ITT)] protocol, ensuring robust and unbiased results. In brief, the missing data were imputed using the Markov Chain Monte Carlo method ensuring that the integrity of the dataset was preserved.

RESULTS

We enrolled a total of 30 patients into the trial with 10 cases into each arm of the trial. Further details on the patient allocation, follow-up summary, and lost to follow-up are given in Figure 1. The characteristics of the patients included in the study are given in Table 1.

Table 1 Characteristics of patients included in the study, *n* (%)

Patient characteristics	Group 1 (bone marrow aspirate concentrate)	Group 2 (pharmacotherapy)	Group 3 (lifestyle modifications)	*P* value
Age (years)	42.2 ± 3.3	40 ± 4.1	39 ± 4.9	0.543
Sperm count	4.75 ± 6.8	7.18 ± 5.3	11.85 ± 4.7	0.064
Sperm motility grade				
Slow progressive motility	0	1 (10)	2 (20)	0.043
Non-progressive motility	3 (30)	8 (80)	5 (50)	
Immotile	4 (40)	1 (10)	3 (30)	
Azoospermia	4 (40)	0	0	

Sperm count

The sperm count at baseline was comparable among the three groups as shown in Table 1. Compared to the baseline, improvement in the sperm count is noted across most of the included patients across all the treatment groups as shown in Table 2. However, neither the BMAC group (P = 0.139) or pharmacotherapy group (P = 0.056) nor the lifestyle modification group (P = 0.112) demonstrated a statistically significant increase in the sperm count at 6 months. However,

Table 2 Evaluation of sperm count among the three groups analyzed

Patient number	Sperm count (in millions)								
	Group 1 (bone marrow aspirate concentrate)			Group 2 (pharmacotherapy)			Group 3 (lifestyle modifications)		
	Baseline	6 months	Δ	Baseline	6 months	Δ	Baseline	6 months	Δ
1	3.3	88	84.7	14	55	41	8	8	0
2	2	22	20	12.5	22	9.5	15	19	4
3	10	24	14	0.5	1	0.5	5	2	-3
4	0	2	2	0.8	1	0.2	16	20	4
5	0	0.8	0.8	7.5	10	2.5	9	10	1
6	0	1	1	2	6	4	18	25	7
7	18	30	12	4	6	2	12	15	3
8	0	N/A	N/A	12	20	8	5	N/A	N/A
9	4	N/A	N/A	5.5	12	6.5	8	N/A	N/A
10	5	N/A	N/A	13	22	9	4	N/A	N/A
Mean	4.7	23.9	19.2	7.1	15.5	3.5	11.8	14.1	2.2

N/A: Not available.

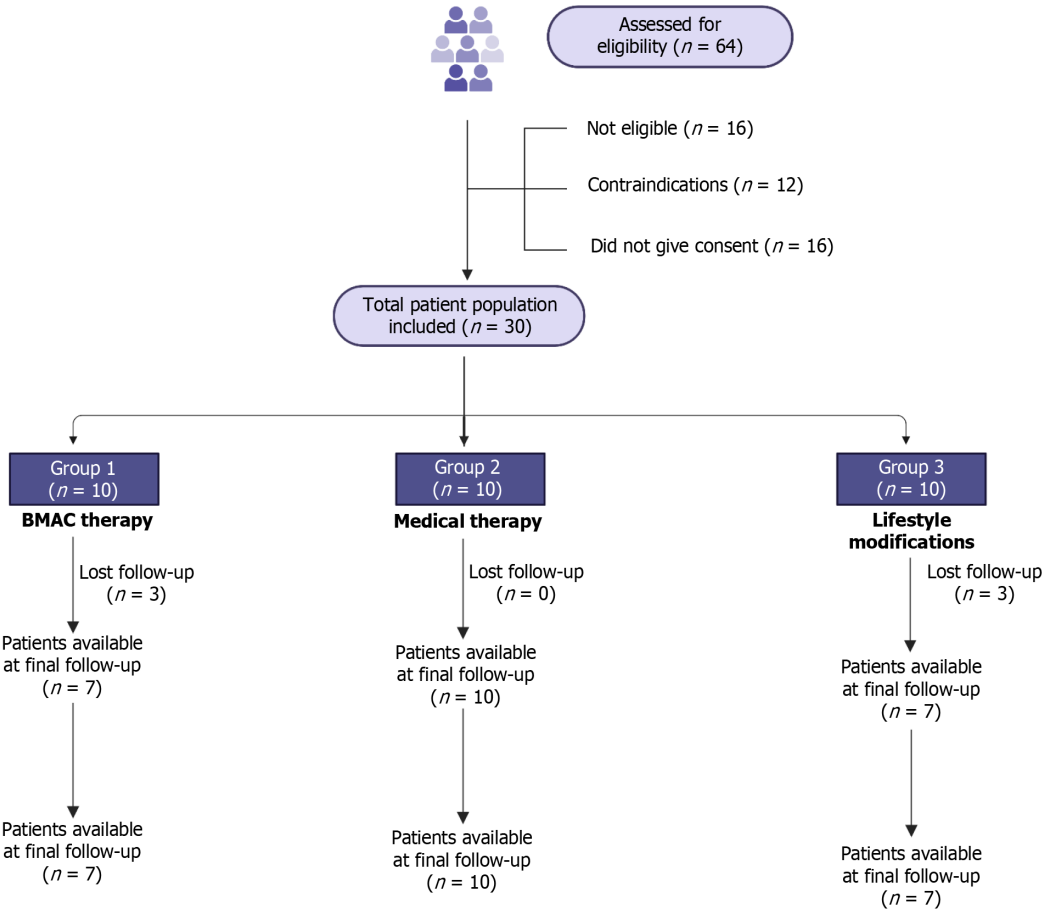


Figure 1 Consolidated Standards of Reporting Trials flow diagram of patients included in the analysis.

comparing the mean differences in the values across the three groups, the BMAC group demonstrated a significant increase in sperm count (mean 19.2 million; $P = 0.001$) compared to the pharmacotherapy group (mean 3.5 million) and lifestyle modification group (mean 2.2 million) at 6 months.

Sperm motility

The sperm motility improvement was recorded at the final follow-up and compared to the baseline. The patients in the BMAC group had a significantly worse motility grade compared to the other two groups at baseline as shown in Table 3. However, significant improvement was noted in the motility grade ($P < 0.001$) only in the BMAC group while no changes were noted in the other groups.

Safety

BMAC group was observed for any potential treatment related complications mentioned above. Of the ten patients, 2 developed donor site pain in the iliac crest that settled with analgesics and no other treatment related complications was noted at the injection site ie. testis.

DISCUSSION

Male infertility is a widespread problem and is caused by factors that reduce the quality and quantity of sperm production as well as transportation. Spermatogenesis is a complex process by which SSC self-renew and differentiate into haploid spermatozoa[34]. In mammals, this process takes place in the seminiferous tubules of the testis, which provide a functional niche for male germ cells and involve three major stages: (1) Mitosis; (2) Meiosis; and (3) Spermatogenesis[35]. Inaccuracies at any stage of spermatogenesis can result in subfertility and infertility[36,37]. In this study, an attempt was made to assess the safety as well as efficacy of BMAC injection in comparison to pharmacological therapy and lifestyle modification to increase sperm number and motility.

Administration of a single dose of BMAC for idiopathic male infertility has revealed that there is an increase in sperm count in comparison to pharmacotherapy and a lifestyle change. Two persons who underwent BMAC therapy upon early diagnosis of oligospermia showed a remarkable increase in sperm count from 3 million to 88 million and 2 million to 22 million in 6 months. The increase in sperm count was noted after 3 months of initial therapy in all groups.

The increase in sperm count in group 1 *i.e.* BMAC therapy may be due to the following reasons. We all know that stem cells are present in BMAC and they have the tendency to regenerate tissues by chemokine, paracrine factors, or by transdifferentiating. Like hematopoiesis, spermatogenesis is also a highly productive stem-cell-based system that is in need for the production of sperm. The basal compartment of the testis and seminiferous tubule has a specialized microenvironment needed for SSC production[38-41]. This concept of microenvironment was proposed by Schofield[42] in 1978 for the hematopoietic cell system. The productivity of sperm is dependent on the stem cell niche which has progeny that undergo several rounds of transit-amplifying divisions before producing the terminally differentiated sperm[43,44].

Bone marrow mononuclear cells prepared from the bone marrow stroma contain MSCs, hematopoietic stem cells, platelets (containing growth factors), and cytokines[45]. There is another population of cells called very small embryonic-like stem cells (VSELs), which are considered to be the descendants of epiblast stem cells and possibly the PGCs that persist into adulthood and undergo asymmetric cell division to replenish the gonadal germ cells throughout life[46,47]. The anti-inflammatory and immunomodulatory properties of bone marrow stem cells (BMSCs) can facilitate the regeneration of germ cells including VSELs and somatic cells including Leydig and Sertoli cells[48].

BMSCs can transdifferentiate to male germ cell-like cells. In male mice, a recent study has demonstrated that BMSCs can differentiate into PGCs and spermatogonia both *in vitro* and *in vivo*[21]. From the literature, it is evident that transplantation of a small number of stem cells is adequate to functionally reconstitute the dependent systems for spermatogenesis. Nayernia *et al*[9] showed for the first time that murine BM-MSCs could differentiate into male germ cells. Yazawa *et al*[49] proved that MSCs can differentiate into steroidogenic cells, such as Leydig cells, both *in vivo* and *in vitro*. More recently, Lue *et al*[48] and Anand *et al*[50] showed that BM-MSCs, transplanted into the testis of a busulfan-treated infertility mouse model, appeared to differentiate into germ cells, Sertoli cells, and Leydig cells. Cho *et al*[51] have reported that BMAC has a cell type that helps in tissue regeneration through their immunomodulatory functions by the secretion of various cytokines and inhibitors of oxidative stress, which further add new horizons for the clinical application of MSCs in male infertility caused by oxidative stress leading to hypoandrogenism and finally altered spermatogenesis.

In this study BMAC injection has increased the sperm count, morphology, and motility more than the empirical treatment and lifestyle modifications during the study period the motility grade was improved only in BMAC-treated patients. This indicates that BMAC contains certain biological factors that help sperm mitochondria for motility. Supporting our study Lue *et al*[48], have reported that MSC from bone marrow when injected in testis home into the basement membrane of seminiferous tubules supplies the growth factors necessary for the proliferation of both germ cell and somatic cells (Leydig and Sertoli cells) and improving the function of sperms by restoring the healthy mitochondrial milieu. Beyond MSCs, BMAC contains a diverse array of growth factors and cytokines[52]. These molecules function as key signaling entities, orchestrating cellular responses and fostering an environment favorable for tissue regeneration and cellular proliferation. Stem and progenitor cells within stem cell niches play a critical role in sustaining tissue and organ regeneration throughout an adult's life. Disruptions in the components of these niches can impair stem cell function and may result in chronic or acute conditions that are challenging to treat. Interestingly, idiopathic male infertility, a common condition lacking targeted treatment options, may be linked to disturbances in the SSC niche. To address this issue,

Table 3 Evaluation of sperm motility grade among the three groups analyzed

Patient number	Sperm motility grade[1]								
	Group 1 (bone marrow aspirate concentrate)			Group 2 (pharmacotherapy)			Group 3 (lifestyle modifications)		
	Baseline	6 months	Δ	Baseline	6 months	Δ	Baseline	6 months	Δ
1	B	A	+1	B	B	-	B	B	-
2	B	A	+1	A	A	-	A	A	-
3	C	B	+1	C	C	-	B	B	-
4	-	B	+3	B	B	-	B	B	-
5	-	B	+3	B	B	-	C	C	-
6	-	C	+1	B	B	-	B	B	-
7	B	A	+1	C	C	-	A	A	-
8	C	N/A	N/A	B	B	-	C	N/A	N/A
9	C	N/A	N/A	B	B	-	B	N/A	N/A
10	C	N/A	N/A	B	B	-	D	N/A	N/A

[1]Normal motility.
A: Slow progressive motility; B: Non progressive motility; C: Immotile; N/A: Not available.

strategies aimed at regenerating damaged stem cell niches deserve exploration. MSCs and their secretome are particularly promising candidates for this task, as they have shown potential in repairing injured stem cell niches[15]. However, the effective use of MSC-based therapies is hindered by limited knowledge of their mechanisms of action that needs further exploration.

This study has several limitations that should be acknowledged. Firstly, the sample size for each treatment arm was relatively small, which may have limited the statistical power to detect subtle differences between groups. Larger patient cohorts are needed in future studies to validate the findings and improve the generalizability of the results. Secondly, complete follow-up data were not available for all participants in certain treatment groups, which could have introduced bias or influenced the reliability of the outcomes. However, to mitigate this, an ITT protocol was adopted in the analysis to ensure that all the participants were included, regardless of protocol adherence. Additionally, the study's follow-up period of six months may not have been sufficient to fully capture long-term effects or sustained improvements in sperm count and motility, particularly for regenerative therapy such as BMAC. Extended follow-up is required to evaluate the durability and clinical significance of the observed improvements. Furthermore, the study design lacked blinding of participants or investigators, which could have introduced observer bias in outcome assessments. Although efforts were made to minimize such bias, future trials should consider a double-blind design for more robust conclusions. Lastly, while the study demonstrated promising results for BMAC in male infertility, the mechanisms underlying its effects, such as potential paracrine signaling or cell fusion, remain incompletely understood. Additional mechanistic studies are required to better elucidate the biological basis of BMAC's therapeutic potential. Further, cost effectiveness analysis needs to be made to explore into the cost aspects of the interventions compared in this study. Despite these limitations, this study provides valuable preliminary evidence supporting the efficacy of autologous BMAC injection for male infertility and underscores the need for further research in this field.

CONCLUSION

This trial highlights the potential of autologous BMAC in male infertility. Despite the absence of significant changes within individual treatment arms, BMAC therapy demonstrated considerable improvement in both sperm count and motility compared to standard pharmacotherapy and lifestyle modifications. These findings underscore the potential role of regenerative medicine in addressing severe oligospermia and azoospermia, warranting further research to solidify its clinical applicability.

FOOTNOTES

Author contributions: Ravi VR designed the research; Devadas AG and Padmanapan DJ performed data collection; Ravi VR, Ramasubramanian S, Muthu S, and Jeyaraman M finalized the manuscript; Jeyaraman N, Ramasubramanian S, Nallakumarasamy A, Muthu S, and Jeyaraman M analyzed the articles for performing review and wrote the manuscript; All of the authors read and approved the final version of the manuscript to be published.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee.

Informed consent statement: All participants provided informed consent.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

Data sharing statement: All data is contained within the manuscript.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Open Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country of origin: India

ORCID number: Ravi Velamoor Rangarajan 0009-0006-7303-8474; Avinash Gandi Devadas 0000-0002-6246-0243; Dhossaradhan Jayakumar Padmanapan 0009-0007-6223-6640; Naveen Jeyaraman 0000-0002-4362-3326; Swaminathan Ramasubramanian 0000-0001-8845-8427; Arulkumar Nallakumarasamy 0000-0002-2445-2883; Sathish Muthu 0000-0002-7143-4354; Madhan Jeyaraman 0000-0002-9045-9493.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Kundu S**, Ali B, Dhillon P. Surging trends of infertility and its behavioural determinants in India. *PLoS One* 2023; **18**: e0289096 [*RCA*] [PMID: 37490506 DOI: 10.1371/journal.pone.0289096] [FullText]
2 **Katole A**, Saoji AV. Prevalence of Primary Infertility and its Associated Risk Factors in Urban Population of Central India: A Community-Based Cross-Sectional Study. *Indian J Community Med* 2019; **44**: 337-341 [*RCA*] [PMID: 31802796 DOI: 10.4103/ijcm.IJCM_7_19] [Full Text] [Full Text(PDF)]
3 **Sharma R**, Bakshi H, Patel P, Patel B, Gajjar S, Dave R, Bapat N, Mehta R, Mehta L, Chaudhary P. Burden of Infertility, Its Risk Factors, Perceptions and Challenges Faced by Women of Peri-urban Community from Ahmedabad City: Mixed Method Study. *Indian J Community Med* 2024; **49**: 687-694 [*RCA*] [PMID: 39421506 DOI: 10.4103/ijcm.ijcm_428_23] [FullText] [Full Text(PDF)]
4 **Agarwal A**, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the globe. *Reprod Biol Endocrinol* 2015; **13**: 37 [*RCA*] [PMID: 25928197 DOI: 10.1186/s12958-015-0032-1] [FullText] [Full Text(PDF)]
5 **Puzuka A**, Alksere B, Gailite L, Erenpreiss J. Idiopathic Infertility as a Feature of Genome Instability. *Life (Basel)* 2021; **11**: 628 [*RCA*] [PMID: 34209597 DOI: 10.3390/life11070628] [FullText] [Full Text(PDF)]
6 **Boeri L**, Kandil H, Ramsay J. Idiopathic male infertility–what are we missing? *Arab J Urol* 2024; **23**: 215-229 [*RCA*] [DOI: 10.1080/20905998.2024.2381972] [FullText] [Full Text(PDF)]
7 **Vasan SS**. Semen analysis and sperm function tests: How much to test? *Indian J Urol* 2011; **27**: 41-48 [*RCA*] [PMID: 21716889 DOI: 10.4103/0970-1591.78424] [FullText] [Full Text(PDF)]
8 **Douglas C**, Parekh N, Kahn LG, Henkel R, Agarwal A. A Novel Approach to Improving the Reliability of Manual Semen Analysis: A Paradigm Shift in the Workup of Infertile Men. *World J Mens Health* 2021; **39**: 172-185 [*RCA*] [PMID: 31749341 DOI: 10.5534/wjmh.190088] [FullText] [Full Text(PDF)]
9 **Nayernia K**, Lee JH, Drusenheimer N, Nolte J, Wulf G, Dressel R, Gromoll J, Engel W. Derivation of male germ cells from bone marrow stem cells. *Lab Invest* 2006; **86**: 654-663 [*RCA*] [PMID: 16652109 DOI: 10.1038/labinvest.3700429] [FullText]
10 **Kubota H**, Brinster RL. Spermatogonial stem cells. *Biol Reprod* 2018; **99**: 52-74 [*RCA*] [PMID: 29617903 DOI: 10.1093/biolre/ioy077] [Full Text]
11 **Cho IK**, Easley CA. Recent Developments in *in vitro* Spermatogenesis and Future Directions. *Reprod Med* 2023; **4**: 215-232 [DOI: 10.3390/reprodmed4030020] [FullText]
12 **Ibtisham F**, Wu J, Xiao M, An L, Banker Z, Nawab A, Zhao Y, Li G. Progress and future prospect of in vitro spermatogenesis. *Oncotarget* 2017; **8**: 66709-66727 [*RCA*] [PMID: 29029549 DOI: 10.18632/oncotarget.19640] [FullText] [Full Text(PDF)]
13 **Leslie SW**, Soon-Sutton TL, Khan MAB. Male Infertility. 2024 Feb 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2025 [PMID: 32965929] [FullText]
14 **Durairajanayagam D**. Lifestyle causes of male infertility. *Arab J Urol* 2018; **16**: 10-20 [*RCA*] [PMID: 29713532 DOI: 10.1016/j.aju.2017.12.004] [FullText] [Full Text(PDF)]
15 **Sagaradze G**, Monakova A, Basalova N, Popov V, Balabanyan V, Efimenko A. Regenerative medicine for male infertility: A focus on stem cell niche injury models. *Biomed J* 2022; **45**: 607-614 [*RCA*] [PMID: 35123107 DOI: 10.1016/j.bj.2022.01.015] [FullText] [Full Text(PDF)]
16 **Zhankina R**, Baghban N, Askarov M, Saipiyeva D, Ibragimov A, Kadirova B, Khoradmehr A, Nabipour I, Shirazi R, Zhanbyrbekuly U, Tamadon A. Mesenchymal stromal/stem cells and their exosomes for restoration of spermatogenesis in non-obstructive azoospermia: a systemic review. *Stem Cell Res Ther* 2021; **12**: 229 [*RCA*] [PMID: 33823925 DOI: 10.1186/s13287-021-02295-9] [FullText] [Full Text(PDF)]
17 **Hajihoseini M**, Vahdati A, Hosseini SE, Mehrabani D, Tamadon A. Induction of spermatogenesis after stem cell therapy of azoospermic

guinea pigs. *Vet arhiv* 2017; **87** [*RCA*] [DOI: 10.24099/vet.arhiv.151209] [FullText]

18 **Roshandel E**, Mehravar M, Nikoonezhad M, Alizadeh AM, Majidi M, Salimi M, Hajifathali A. Cell-Based Therapy Approaches in Treatment of Non-obstructive Azoospermia. *Reprod Sci* 2023; **30**: 1482-1494 [*RCA*] [PMID: 36380137 DOI: 10.1007/s43032-022-01115-6] [FullText]

19 **Zhang D**, Liu X, Peng J, He D, Lin T, Zhu J, Li X, Zhang Y, Wei G. Potential spermatogenesis recovery with bone marrow mesenchymal stem cells in an azoospermic rat model. *Int J Mol Sci* 2014; **15**: 13151-13165 [*RCA*] [PMID: 25062349 DOI: 10.3390/ijms150813151] [FullText] [Full Text(PDF)]

20 **Karimaghai N**, Tamadon A, Rahmanifar F, Mehrabani D, Raayat Jahromi A, Zare S, Khodabandeh Z, Razeghian Jahromi I, Koohi-Hoseinabadi O, Dianatpour M. Spermatogenesis after transplantation of adipose tissue-derived mesenchymal stem cells in busulfan-induced azoospermic hamster. *Iran J Basic Med Sci* 2018; **21**: 660-667 [*RCA*] [PMID: 30140403 DOI: 10.22038/IJBMS.2018.29040.7010] [FullText] [Full Text(PDF)]

21 **Cakici C**, Buyrukcu B, Duruksu G, Haliloglu AH, Aksoy A, Isık A, Uludag O, Ustun H, Subası C, Karaoz E. Recovery of fertility in azoospermia rats after injection of adipose-tissue-derived mesenchymal stem cells: the sperm generation. *Biomed Res Int* 2013; **2013**: 529589 [*RCA*] [PMID: 23509736 DOI: 10.1155/2013/529589] [FullText] [Full Text(PDF)]

22 **Mohamed Rasheed ZB**, Nordin F, Wan Kamarul Zaman WS, Tan YF, Abd Aziz NH. Autologous Human Mesenchymal Stem Cell-Based Therapy in Infertility: New Strategies and Future Perspectives. *Biology (Basel)* 2023; **12**: 108 [*RCA*] [PMID: 36671799 DOI: 10.3390/biology12010108] [FullText]

23 **Gauthier-Fisher A**, Kauffman A, Librach CL. Potential use of stem cells for fertility preservation. *Andrology* 2020; **8**: 862-878 [*RCA*] [PMID: 31560823 DOI: 10.1111/andr.12713] [FullText]

24 **Chen H**, Tang QL, Wu XY, Xie LC, Lin LM, Ho GY, Ma L. Differentiation of human umbilical cord mesenchymal stem cells into germ-like cells in mouse seminiferous tubules. *Mol Med Rep* 2015; **12**: 819-828 [*RCA*] [PMID: 25815600 DOI: 10.3892/mmr.2015.3528] [FullText] [Full Text(PDF)]

25 **Fan XL**, Zhang Y, Li X, Fu QL. Mechanisms underlying the protective effects of mesenchymal stem cell-based therapy. *Cell Mol Life Sci* 2020; **77**: 2771-2794 [*RCA*] [PMID: 31965214 DOI: 10.1007/s00018-020-03454-6] [FullText] [Full Text(PDF)]

26 **Sagaradze G**, Basalova N, Kirpatovsky V, Ohobotov D, Nimiritsky P, Grigorieva O, Popov V, Kamalov A, Tkachuk V, Efimenko A. A magic kick for regeneration: role of mesenchymal stromal cell secretome in spermatogonial stem cell niche recovery. *Stem Cell Res Ther* 2019; **10**: 342 [*RCA*] [PMID: 31753023 DOI: 10.1186/s13287-019-1479-3] [FullText] [Full Text(PDF)]

27 **Hsiao CH**, Ji AT, Chang CC, Cheng CJ, Lee LM, Ho JH. Local injection of mesenchymal stem cells protects testicular torsion-induced germ cell injury. *Stem Cell Res Ther* 2015; **6**: 113 [*RCA*] [PMID: 26025454 DOI: 10.1186/s13287-015-0079-0] [FullText] [Full Text(PDF)]

28 **Porubska B**, Plevakova M, Fikarova N, Vasek D, Somova V, Sanovec O, Simonik O, Komrskova K, Krylov V, Tlapakova T, Krulova M, Krulova M. Therapeutic potential of Sertoli cells in vivo: alleviation of acute inflammation and improvement of sperm quality. *Stem Cell Res Ther* 2024; **15**: 282 [*RCA*] [PMID: 39227878 DOI: 10.1186/s13287-024-03897-9] [FullText]

29 **Kaur G**, Long CR, Dufour JM. Genetically engineered immune privileged Sertoli cells: A new road to cell based gene therapy. *Spermatogenesis* 2012; **2**: 23-31 [*RCA*] [PMID: 22553487 DOI: 10.4161/spmg.19119] [FullText] [Full Text(PDF)]

30 **Song N**, Scholtemeijer M, Shah K. Mesenchymal Stem Cell Immunomodulation: Mechanisms and Therapeutic Potential. *Trends Pharmacol Sci* 2020; **41**: 653-664 [*RCA*] [PMID: 32709406 DOI: 10.1016/j.tips.2020.06.009] [FullText]

31 **Rahmanifar F**, Tamadon A, Mehrabani D, Zare S, Abasi S, Keshavarz S, Dianatpour M, Khodabandeh Z, Jahromi IR, Koohi-Hoseinabadi O. Histomorphometric evaluation of treatment of rat azoosper-mic seminiferous tubules by allotransplantation of bone marrow-derived mesenchymal stem cells. *Iran J Basic Med Sci* 2016; **19**: 653-661 [*RCA*] [PMID: 27482347] [FullText] [Full Text(PDF)]

32 **Tamadon A**, Mehrabani D, Rahmanifar F, Jahromi AR, Panahi M, Zare S, Khodabandeh Z, Jahromi IR, Tanideh N, Dianatpour M, Ramzi M, Koohi-Hoseinabadi O. Induction of Spermatogenesis by Bone Marrow-derived Mesenchymal Stem Cells in Busulfan-induced Azoospermia in Hamster. *Int J Stem Cells* 2015; **8**: 134-145 [*RCA*] [PMID: 26634062 DOI: 10.15283/ijsc.2015.8.2.134] [FullText] [Full Text(PDF)]

33 **Levine H**, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Jolles M, Pinotti R, Swan SH. Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. *Hum Reprod Update* 2023; **29**: 157-176 [*RCA*] [PMID: 36377604 DOI: 10.1093/humupd/dmac035] [FullText]

34 **Subash SK**, Kumar PG. Spermatogonial stem cells: A story of self-renewal and differentiation. *Front Biosci (Landmark Ed)* 2021; **26**: 163-205 [*RCA*] [PMID: 33049667 DOI: 10.2741/4891] [FullText]

35 **Xi HM**, Ren YJ, Ren F, Li Y, Feng TY, Wang Z, Du YQ, Zhang LK, Hu JH. Recent advances in isolation, identification, and culture of mammalian spermatogonial stem cells. *Asian J Androl* 2022; **24**: 5-14 [*RCA*] [PMID: 34135169 DOI: 10.4103/aja.aja_41_21] [FullText] [Full Text(PDF)]

36 **Kita K**, Watanabe T, Ohsaka K, Hayashi H, Kubota Y, Nagashima Y, Aoki I, Taniguchi H, Noce T, Inoue K, Miki H, Ogonuki N, Tanaka H, Ogura A, Ogawa T. Production of functional spermatids from mouse germline stem cells in ectopically reconstituted seminiferous tubules. *Biol Reprod* 2007; **76**: 211-217 [*RCA*] [PMID: 17065598 DOI: 10.1095/biolreprod.106.056895] [FullText]

37 **Zhu Y**, Hu HL, Li P, Yang S, Zhang W, Ding H, Tian RH, Ning Y, Zhang LL, Guo XZ, Shi ZP, Li Z, He Z. Generation of male germ cells from induced pluripotent stem cells (iPS cells): an in vitro and in vivo study. *Asian J Androl* 2012; **14**: 574-579 [*RCA*] [PMID: 22504877 DOI: 10.1038/aja.2012.3] [FullText]

38 **Diao L**, Turek PJ, John CM, Fang F, Reijo Pera RA. Roles of Spermatogonial Stem Cells in Spermatogenesis and Fertility Restoration. *Front Endocrinol (Lausanne)* 2022; **13**: 895528 [*RCA*] [PMID: 35634498 DOI: 10.3389/fendo.2022.895528] [FullText] [Full Text(PDF)]

39 **Sanou I**, van Maaren J, Eliveld J, Lei Q, Meißner A, de Melker AA, Hamer G, van Pelt AMM, Mulder CL. Spermatogonial Stem Cell-Based Therapies: Taking Preclinical Research to the Next Level. *Front Endocrinol (Lausanne)* 2022; **13**: 850219 [*RCA*] [PMID: 35444616 DOI: 10.3389/fendo.2022.850219] [FullText] [Full Text(PDF)]

40 **Abdelaal NE**, Tanga BM, Abdelgawad M, Allam S, Fathi M, Saadeldin IM, Bang S, Cho J. Cellular Therapy *via* Spermatogonial Stem Cells for Treating Impaired Spermatogenesis, Non-Obstructive Azoospermia. *Cells* 2021; **10**: 1779 [*RCA*] [PMID: 34359947 DOI: 10.3390/cells10071779] [FullText] [Full Text(PDF)]

41 **Damyanova KB**, Nixon B, Johnston SD, Gambini A, Benitez PP, Lord T. Spermatogonial stem cell technologies: applications from human medicine to wildlife conservation†. *Biol Reprod* 2024; **111**: 757-779 [*RCA*] [PMID: 38993049 DOI: 10.1093/biolre/ioae109] [FullText]

42 **Schofield R**. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. *Blood Cells* 1978; **4**: 7-25 [PMID: 747780] [FullText]

43 **Hermann BP**, Sukhwani M, Winkler F, Pascarella JN, Peters KA, Sheng Y, Valli H, Rodriguez M, Ezzelarab M, Dargo G, Peterson K,

Masterson K, Ramsey C, Ward T, Lienesch M, Volk A, Cooper DK, Thomson AW, Kiss JE, Penedo MC, Schatten GP, Mitalipov S, Orwig KE. Spermatogonial stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm. *Cell Stem Cell* 2012; **11**: 715-726 [*RCA*] [PMID: 23122294 DOI: 10.1016/j.stem.2012.07.017] [FullText]

44 **Fayomi AP**, Orwig KE. Spermatogonial stem cells and spermatogenesis in mice, monkeys and men. *Stem Cell Res* 2018; **29**: 207-214 [*RCA*] [PMID: 29730571 DOI: 10.1016/j.scr.2018.04.009] [FullText] [Full Text(PDF)]

45 **Henrich D**, Verboket R, Schaible A, Kontradowitz K, Oppermann E, Brune JC, Nau C, Meier S, Bonig H, Marzi I, Seebach C. Characterization of bone marrow mononuclear cells on biomaterials for bone tissue engineering in vitro. *Biomed Res Int* 2015; **2015**: 762407 [*RCA*] [PMID: 25802865 DOI: 10.1155/2015/762407] [FullText] [Full Text(PDF)]

46 **Bhartiya D**, Unni S, Parte S, Anand S. Very small embryonic-like stem cells: implications in reproductive biology. *Biomed Res Int* 2013; **2013**: 682326 [*RCA*] [PMID: 23509758 DOI: 10.1155/2013/682326] [FullText] [Full Text(PDF)]

47 **Ratajczak MZ**, Ratajczak J, Kucia M. Germinal Origin of Very Small Embryonic-Like Stem Cells (VSELs): Relation to Primordial Germ Cells. In: Virant-Klun I, editor. Stem Cell Biology and Regenerative Medicine. Berlin: Springer, 2022 [DOI: 10.1007/978-3-030-90111-0_11] [FullText]

48 **Lue Y**, Erkkila K, Liu PY, Ma K, Wang C, Hikim AS, Swerdloff RS. Fate of bone marrow stem cells transplanted into the testis: potential implication for men with testicular failure. *Am J Pathol* 2007; **170**: 899-908 [*RCA*] [PMID: 17322375 DOI: 10.2353/ajpath.2007.060543] [Full Text]

49 **Yazawa T**, Mizutani T, Yamada K, Kawata H, Sekiguchi T, Yoshino M, Kajitani T, Shou Z, Umezawa A, Miyamoto K. Differentiation of adult stem cells derived from bone marrow stroma into Leydig or adrenocortical cells. *Endocrinology* 2006; **147**: 4104-4111 [*RCA*] [PMID: 16728492 DOI: 10.1210/en.2006-0162] [FullText]

50 **Anand S**, Bhartiya D, Sriraman K, Mallick A. Underlying Mechanisms that Restore Spermatogenesis on Transplanting Healthy Niche Cells in Busulphan Treated Mouse Testis. *Stem Cell Rev Rep* 2016; **12**: 682-697 [*RCA*] [PMID: 27663915 DOI: 10.1007/s12015-016-9685-1] [Full Text]

51 **Cho KS**, Kim YW, Kang MJ, Park HY, Hong SL, Roh HJ. Immunomodulatory Effect of Mesenchymal Stem Cells on T Lymphocyte and Cytokine Expression in Nasal Polyps. *Otolaryngol Head Neck Surg* 2014; **150**: 1062-1070 [*RCA*] [PMID: 24627407 DOI: 10.1177/0194599814525751] [FullText]

52 **Muthu S**, Jeyaraman M, Narula A, Ravi VR, Gandi A, Khanna M, Maffulli N, Gupta A. Factors Influencing the Yield of Progenitor Cells in Bone Marrow Aspiration Concentrate-A Retrospective Analysis of 58 Patients. *Biomedicines* 2023; **11**: 738 [*RCA*] [PMID: 36979718 DOI: 10.3390/biomedicines11030738] [FullText] [Full Text(PDF)]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2025 Baishideng Publishing Group Inc. All rights reserved.