An update on the role of medical treatment including antioxidant therapy in varicocele

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Varicocele-associated male infertility has classically been managed using surgery or assisted reproductive techniques. With increasing evidence of oxidative stress as a pathophysiological factor in varicocele-associated infertility, medical therapy especially antioxidants might become a treatment option with lower risks. We reviewed the existing literature on the role of various medical agents in the management of male infertility attributed to varicoceles. Medical therapy is typically evaluated in three different situations such as (a) comparison of two drugs or one drug with placebo, (b) comparison of drugs versus surgery, and (c) comparison of drugs as adjuvant therapy with surgery versus drug therapy alone. Due to heterogeneity of data and lack of well-conducted studies, there is insufficient data to recommend routine use of medical therapy for men with varicocele-associated infertility and surgery remains the treatment of choice. Pregnancy and live birth rates are usually not reported in most studies and mere improvement in sperm parameters or antioxidant capacity is insufficient to support its routine use. Antioxidant therapy is a potential option due to its theoretical benefit, data from preclinical studies, and lack of major side effects. Adjuvant therapy with antioxidants after surgical repair of varicocele may improve the outcome and is a potential area for further research.

Asian Journal of Andrology (2016) 18, 222–228; doi: 10.4103/1008-682X.171657; published online: 8 January 2016

Keywords: antioxidant therapy; drug therapy; male infertility; varicocele

INTRODUCTION

Even though varicoceles are considered a major cause of male infertility, the fact that not all men with varicoceles are infertile and repairing a varicocele does not always result in improved fertility has fueled the varicocele debate. The pathophysiology behind varicocele-induced infertility has been extensively studied but definite mechanisms are unclear. Varicocele-induced oxidative stress, hormonal disturbances, scrotal hyperthermia, reflux of renal and adrenal metabolites, and testicular hypo perfusion are among major mechanisms.

Oxidative stress appears to be the central mediator of testicular damage in varicoceles, and the exact pathophysiology behind varicocele-induced infertility is yet to be elucidated. Heat stress associated with varicocele is known to induce mitochondrial, plasma membrane, cytoplasmic, and peroxisomal reactive oxygen species including nitrous oxide (NO) and hydrogen peroxide (H₂O₂).

Testicular ischemia can also occur due to increased venous hydrostatic pressure in varicocele, which leads to increased expression of cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6), and hormones such as leptin. These agents induce generation of reactive oxygen species and impair fertility. Infertile men with or without varicoceles have increased seminal reactive oxygen species but such levels are higher in the former, suggesting that varicoceles exacerbate oxidative stress. The grade of varicocele has also been correlated directly with the level of oxidative stress. Antioxidant therapy that helps negate oxidative stress could thus improve varicocele-associated infertility.

Surgery remains the mainstay of management of varicocele. Varicocelectomy can be performed with open, laparoscopic, or microsurgical techniques. The procedure can also be done with different approaches including retroperitoneal, inguinal, subinguinal, and scrotal. Percutaneous embolisation is another interventional option. However, all such interventions are associated with complications including potential testicular atrophy and, in the absence of identifiable predictors of success, there is an understandable desire to seek less invasive treatments. Assisted reproduction offers an alternative to surgery but is associated with risks, costs, and possible need for repetitive interventions. Medical management, including antioxidants, could offer a potential solution with lower risks given the increasing evidence suggesting the role of oxidative stress in varicocele-induced infertility. In this article, we review the existing literature on the role of various medical agents in male infertility attributed to varicoceles.

MATERIALS AND METHODS

Search strategy

Between March and April 2015, PubMed/Medline® database was searched using the key words such as varicocele, male infertility, treatment, drug therapy, antioxidant therapy, and hormonal therapy for articles published after 1985.

Eligibility criteria

Articles involving human studies were included. Articles published in languages other than English were also considered. Data that were solely published in conference or meeting proceedings, websites, or books were not included. Case reports and reviews were gathered...
to screen their reference lists for additional relevant articles. For articles published in English, full texts were sought while for articles in languages other than English, only the English language abstracts were accessed.

**Study selection**
Full texts were retrieved through either the journal access from the library or a request to the author. If full-text access was not accessible, the abstracts were reviewed.

**Data collection process and data items**
An initial screening of the articles suggested that most studies were performed in one of the three settings such as (a) comparison of two drugs or one with a placebo, (b) comparison of drugs versus surgery, and (c) comparison of drugs as adjuvant after surgery versus surgery or drugs alone. This review looks at these studies in three different settings.

**RESULTS**
A total of 25 manuscripts describing clinical impact of various medical agents on varicocele-associated infertility were included in the review. Some manuscripts were included under more than one heading as they were used in multiple settings in the same report. Full texts were retrieved for 14 manuscripts and only abstracts could be retrieved for the remaining 11 studies.

**Drugs as sole therapy**

**Hormonal agents**
Varicoceles have been shown to be associated with low testosterone. It, therefore, seems logical that therapies that manipulate the hormonal milieu may result in improvement in semen parameters. However, there are little data on androgenic hormones in varicocele-associated infertility (Table 1). In 1999, Radicioni and Schwarzenberg treated 20 adolescents and young adults with idiopathic, unilateral left varicocele with purified urinary FSH 75 IU thrice weekly for 3 months and reported a significant improvement in sperm density per ml (from $38 \times 10^6$ to $49 \times 10^6$), total sperm number per ejaculate with forward motility ($37 \times 10^6$ to $48 \times 10^6$), and a decrease of atypical forms (53% to 38%).

Kallikrein, which is thought to play a role in the management of male infertility. Increased oxidative stress decreases the availability of this coenzyme in oxidative phosphorylation. Hence, exogenous supplementation might increase its content in semen and improve sperm characteristics. Festa et al. studied a subclinical left varicocele to palpable varicocele (11% vs 21%, $P < 0.05$) in sperm parameters associated with clinical varicocele and subclinical varicoceles, and clinical varicoceles. In one group, improvement occurred in patients with subclinical varicocele and not with clinical varicocele.

Oliva et al. studied the role of combination therapy of pentoxifylline (1200 mg per day) + zinc (66 mg per day) + folic acid (5 mg per day) administered to 36 men with clinical varicocele-associated infertility and, at least, one abnormal semen parameter for 3 months. The authors found a significant improvement ($P < 0.05$) in the proportion of morphologically normal sperm that persisted at least for 4 weeks after discontinuation of therapy. This was an open-labeled, uncontrolled study and did not report pregnancy data, thus limiting the value of the results.

Coenzyme Q10 is another antioxidant which has been found to play a role in the management of male infertility. Increased oxidative stress decreases the availability of this coenzyme in oxidative phosphorylation. Hence, exogenous supplementation might increase its content in semen and improve sperm characteristics. Festa et al. in an open-labeled, uncontrolled pilot study evaluated the antioxidant capacity of seminal plasma before and after supplementation of coenzyme Q10 100 mg per day for 12 weeks in patients with male infertility associated with low-grade varicocele. They found significant increase in total antioxidant capacity ($P < 0.01$), significant improvements in sperm density ($P = 0.03$) and forward sperm motility ($P = 0.03$). However, they did not measure the persistence of these changes after discontinuation of therapy and did not report any pregnancy owing to the short period of the study.

Bioflavonoid, a plant pigment responsible for coloring of flowers, is another class of antioxidants shown to be effective in varicocele with altered sperm parameters. These agents possibly prolong the activity of peripheral norepinephrine, increase the mechanical tension and calcium sensitivity of contractile apparatus, thus improving venous tone in varicoceles. Zampieri et al. studied 168 adolescent boys with a subclinical left-sided varicoceles in a longitudinal observational study and demonstrated significantly slower rate of progression of subclinical varicocele to palpable varicocele (11% vs 31%, $P = 0.002$). The authors also reported higher resolution rate (41% vs 31%, $P < 0.05$) with cyclical therapy of semisynthetic derivative of bioflavanoid (O-β-hydroxyethyl rutoside) at 1000 mg per day thrice monthly for 1 year. However, the drug had no protective effects against testicular growth arrest.

Another derivative of bioflavanoid in the form of micronized purified flavonoid fraction (MPFF, commonly available as Daflon) was also evaluated to study its effect on pain score, spermogram, and color Doppler parameters in patients with clinical painful varicocele.
Medical therapy in varicocele infertility

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Table 1: Studies comparing medical agents as sole therapy in management of varicocele-associated infertility

| Author and reference | Year | Study design | Group labels | n   | Dose and duration | Outcome parameters | Results |
|----------------------|------|--------------|--------------|-----|-------------------|--------------------|---------|
| **Hormonal agents**  |      |              |              |     |                   |                    |         |
| Radicioni and Schwarzenberg⁸ | 1999 | Prospective uncontrolled study | FSH          | 20  | 75 IU (subcutaneous) thrice per week × 3 months | Sperm density     | Significant improvement |
|                      |      |              |              | 20  | 75 IU (subcutaneous) thrice per week × 3 months | Sperm forward motility | Significant improvement |
|                      |      |              |              |     |                   | Sperm atypical forms | Significant decline |
| **Antioxidants**     |      |              |              |     |                   |                    |         |
| Mićić et al.⁹        | 1990 | RCT          | Kallikrein    | 38  | 600 IU per day × 3 months | Sperm motility     | Significant improvement in treated versus control group |
|                      |      |              | Placebo      | 27  |                   | Sperm morphology   | Significant improvement in treated versus control group |
| Cavallini et al.¹⁰   | 2003 | RCT          | Cinnoxicam    | 55  | 30 mg suppository every 4 days × 12 months | Seminal parameters | Significant improvement in grade 3 varicocele only in treated group after 2 months of therapy; therapy cessation caused a decline to the baseline values |
|                      |      |              | Glycerine suppository every 4 days × 12 months | 54  |                   |                    |       |
| **Cavallini et al.¹¹  | 2004 | Prospective controlled study | L-carnitine + acetyl L-carnitine (Group 1) | 62 varicocele + 39 iOAT | (1 g per day) × 6 months | Seminal parameters at 3 and 6 months | Significant improvement in Group 1 in those patients with small to moderate varicocele grades, and in Group 2 in patients with all varicocele grades. Overall, improvement was better in Group 2 than Group 1. All sperm parameters fell to baseline after therapy suspension |
|                      |      |              | L-carnitine + L-carnitine + cinnoxicam (Group 2) | 62 varicocele + 44 iOAT | (1 g per day) + cinnoxicam 30 mg per day suppository every 4 days × 6 months | Pregnancy rate | 21.8% in Group 1 versus 38% in Group 2 versus 1.7% in Group 3 (P<0.01) |
|                      |      |              |                |     |                   |                    |     |
| Kiliç et al.¹⁵        | 2005 | Open uncontrolled study | MPFF          | 16  | 1 g per day × 6 months | Relief of varicocele-associated pain | Significant improvement (P<0.001) |
|                      |      |              |                |     |                   | Sperm motility     | Significant improvement (P=0.009) |
|                      |      |              |                |     |                   | Color Doppler parameters | Significant improvement (P=0.003) |
| Oliva et al.¹²        | 2009 | Open uncontrolled study | Pentoxifylline + zinc + folic acid | 36  | Pentoxifylline (1200 mg) + zinc (66 mg) + folic acid (5 mg) × 3 months | Sperm morphology | Significant improvement that persisted at least 4 weeks after end of treatment |
|                      |      |              |                |     |                   |                    |       |
| Soylemez et al.¹⁶     | 2012 | RCT          | MPFF          | 20  | 1 g per day × 6 months | Relief of varicocele-associated pain | Significant improvement in medical therapy group (P<0.001) |
|                      |      |              |                |     |                   | Sperm motility     | Significant improvement in medical therapy group (P=0.015) |
|                      |      |              |                |     |                   | Color Doppler parameters | Significant improvement in medical therapy group (P<0.001) |
| Festa et al.¹³        | 2014 | Open prospective uncontrolled pilot study | Coenzyme Q | 38  | 100 mg per day × 3 months | Sperm parameters | Significant improvement |
| **Chinese medicine**  |      |              |              |     |                   |                    |         |
| *Ishikawa et al.¹⁸    | 1996 | Prospective uncontrolled study | Guizhi-Fuling Wan | 37  | 7.5 g per day × 3 months | Varicocele disappearance rate | 80% Improvement in 71.4% cases |
|                      |      |              |                |     |                   | Sperm concentration | Improvement in 62.1% cases |
|                      |      |              |                |     |                   | Sperm motility     |                                               |
|                      |      |              |                |     |                   | Sperm density      | Significant improvement in medical therapy group (57.5% vs 38.5%) |
| *Fang et al.¹⁰        | 2010 | RCT          | Escin         | 106 | 30 mg BD × 2 months | Sperm motility     | No change |
|                      |      |              |                |     |                   |                    |       |

FSH: follicle stimulating hormone; iOAT: idiopathic oligoasthenoteratozoospermia; MPFF: micronised purified flavonoid fraction; RCT: randomized controlled trial; *abstract only

**Asian Journal of Andrology**
after treatment for 6 months. It was found that medical therapy resulted in significant relief of varicocele-associated pain ($P < 0.001$), improvement in color Doppler parameters (i.e., decrease in the reflux time of left spermatic vein during Valsalva maneuver; $P = 0.003$), and improvement in sperm motility ($P = 0.009$). It did not lead to any improvement in total sperm count, sperm concentration, morphology, and semen volume. Later, the same group conducted a placebo-controlled randomized controlled trial to study the effects of MPFF at dose of 1000 mg per day for 6 months in 40 patients with clinical varicocele and sperm concentration $>20$ million ml$^{-1}$. They reported significant improvement in pain ($P < 0.001$), color Doppler parameters ($P < 0.001$), and sperm motility ($P = 0.015$) at the end of the treatment. None of these aforementioned studies have looked at varicocele-associated infertility, and their end-points have focused on pain and Doppler parameters.

**Chinese medicine**

A myriad of Chinese medicines with antioxidant and anti-inflammatory activity have been studied as possible therapeutic agents for management of varicocele and male infertility. *Qianjing* is a herbal medicine observed to improve epididymal microenvironment and seminal parameters by increasing gluthathione peroxidase and decreasing malondialdehyde in seminal plasma in rats. Another anti-inflammatory agent and antioxidant, *Guizhi Fuling Wan*, was shown to improve sperm concentration and sperm motility in patients suffering from varicocele and male infertility. Another extensively used Chinese agent, *Escin*, derived from seed extract of *Aesculus hippocastanum*, is an anti-inflammatory and anti-edema agent that enhances glucocorticoid and Prostaglandin F$_2$α activity and decreases Nuclear Factor-kappa β (NF-κB) expression. Fang et al. compared 106 patients with clinical or subclinical varicocele-associated infertility who received escin 60 mg d$^{-1}$ for two months with controls. All the patients received composite medicines favorable for sperm quality. They found significant improvements in sperm density (57.5% vs 38.5%, $P < 0.05$) and sperm motility (55.7% vs 46.2%, $P < 0.05$). They also reported better improvements in these sperm parameters in patients with moderate grade of varicocele as compared to severe grade.

**Drugs versus surgery**

**Hormonal agents**

Antiestrogens and gonadotropins enhance spermatogenesis stimulation and have been compared to varicocelectomy (Table 2). Unal et al. randomized 42 infertile men with left subclinical varicocele to either clomiphene citrate 50 mg per day for 6 months or surgical management. Surgical management involved open ligation of spermatic vein (subinguinal varicocelectomy). They reported that varicocelectomy led to significant improvements in terms of sperm density and motility ($P < 0.05$), but there was no significant difference between medical or surgical management in terms of sperm density ($P = 0.66$), sperm morphology ($P = 0.37$), and sperm motility ($P = 0.31$) 6 months after surgery or initiation of medical therapy. Pregnancy was recorded in two cases of the surgical group while only one case in medical group (12.5% vs 6.7%, $P = 0.58$). They concluded no statistical difference in overall outcome in medical or surgical management of varicocele-associated infertility. De Rose et al. compared gonadotropins in the form of menotropin (hMG, human menopausal gonadotropin) versus varicocelectomy in a small trial to assess spermatogenesis stimulation. Twenty patients received menotropin for 3 months while 20 patients underwent subinguinal varicocelectomy. There was a significant improvement in sperm characteristics in the medical therapy group after 12 months follow-up.

In term of pregnancy rate, 47% cases in medical therapy group reported pregnancy compared with 27.7% in the surgical group in a follow-up of 12 months ($P < 0.05$).

**Antioxidants**

Cinnoxicam, an anti-inflammatory agent, inhibits reactive oxygen species and prostaglandin synthesis which are often raised in varicocele. Cavallini et al. compared 41 patients with clinical or subclinical varicocele-associated infertility receiving cinnoxicam treatment at a dose of 30 mg suppository every 4 days for 12 months with 61 similar patients undergoing microsurgical subinguinal venous ligation. Surgery significantly improved sperm values in men with moderate to severe varicocele within 4 months. Cinnoxicam significantly improved sperm quality in patients with moderate varicocele only. The improvement in medical group declined to baseline after cessation of therapy. They did not report pregnancy rate in either group.

In another study including a large cohort of infertile men with varicocele, Gamidov et al. treated 728 patients with bilateral microsurgical subinguinal varicocelectomy and 107 with antioxidant combinations (clomiphene citrate, Vitamins A and E, selenium, L-carnitine, pentoxifylline, and antioxidants) for 3–6 months and 56 patients served as untreated controls. Within a follow-up of 3–12 months, they reported an increase in sperm concentration after both surgery and drug therapy (70% patients vs 30% patients). Natural pregnancy was recorded in 47% of the patients in the surgery group and 21% in the medical therapy compared with 3.6% in the untreated group.

**Chinese medicine**

In a three-armed randomized controlled study of 219 subjects, *Escin* in a dose of 60 mg per day for 2 months was compared with surgery and controls who received no treatment. There was an improvement in sperm density in all the three groups: 69% of the cases undergoing varicocelectomy only. The improvement in medical group declined to baseline after cessation of therapy. They did not report pregnancy rate in either group.

**Adjuvant drug therapy**

Medical therapy as adjuvant to surgical management of varicocele is often used to maximize benefits of both modalities. Multiple studies have compared adjuvant therapy after surgery with medical therapy or surgery alone. Table 3 lists studies comparing adjuvant medical therapy with medical therapy alone.

**Hormonal agents**

Gonadotropins and antiestrogens have been used as adjuvant therapy after varicocelectomy. In a controlled trial of 60 men divided into three arms, Menotropin use after surgery was found to be superior to either Menotropin or subinguinal varicocelectomy alone. Combined therapy not only significantly improved sperm concentration, motility, and morphology 6 months and 12 months after surgery ($P < 0.05$) but also led to significantly higher pregnancy rate (45% with combination therapy vs 42% with medical therapy and 27.7% with varicocelectomy alone; $P < 0.05$). Kadioglu et al. studied the role of tamoxifen 20 mg per day for 6 months as adjuvant therapy for spermatogenesis stimulation after varicocelectomy in 84 infertile patients with clinical varicoceles. The authors showed significant increase in sperm concentration from 13.5 to 18 million ml$^{-1}$ in normogonadotropic patients.
Table 2: Studies comparing roles of medical agents versus surgery in management of varicocele-associated infertility

| Author          | Year | Study design     | Group labels                      | n     | Dose, duration       | Outcome parameters                  | Results                                      |
|-----------------|------|------------------|-----------------------------------|-------|----------------------|--------------------------------------|---------------------------------------------|
| **Hormonal agents**                                                                                       |
| Unal et al.21   | 2001 | Prospective      | Varicocelectomy (Group 1)         | 21    | -                    | Sperm parameters                     | Improved in both groups, but more significantly in Group 1 (12.5% (Group 1) vs 6.7% (Group 2) (P=0.58)) |
|                 |      | randomized study | Clomiphene citrate (Group 2)      | 21    | 50 mg per day × 6 months | Pregnancy rate                      | 12.5% in Group 1 versus 6.7% in Group 2      |
| De Rose et al.22| 2003 | Prospective      | Menotropin (Group 1)              | 20    | Dose × 3 months      | Seminal parameters at 3 months       | Significant improvement in Group 1 only     |
|                 |      | randomized study | Varicocelectomy (Group 2)         | 20    | -                    | Seminal parameters at 6 months       | Significant improvement in Group 1 compared with Group 2 |
|                 |      |                  |                                   |       |                      | Seminal parameters at 12 months      | Significant improvement in Group 1 compared with Group 2 |
|                 |      |                  |                                   |       |                      | Pregnancy rate at 6 months           | 42% in Group 1 versus 22.2% in Group 2      |
|                 |      |                  |                                   |       |                      | Pregnancy rate at 12 months          | 47% in Group 1 versus 27.7% in Group 2      |
| **Antioxidants**                                                                                         |
| Cavallini et al.10 | 2003 | RCT              | Varicocelectomy (Group 1)         | 41    | -                    | Seminal parameters                   | Significant improvement in all grades of varicocele in Group 1 after 4 months; Significant improvement in grade 3 varicocele only in Group 2 after 2 months of therapy; therapy cessation caused a decline to the baseline values |
|                 |      |                  | Cinnoxim (Group 2)                | 55    | 30 mg suppository every 4 days × 12 months |                  |                                             |
| **Chinese medicine**                                                                                    |
| *Fang et al.20  | 2010 | RCT              | Escin (Group 1)                   | 106   | 30 mg BO × 2 months  | Sperm density                        | Significant improvement in both groups (57.5% in Group 1 and 68.8% in Group 2) |
| **Miscellaneous**                                                                                       |
| *Gamidov et al.23| 2012 | Prospective      | Surgery (microsurgical subinguinal varicocelectomy) | 728   | -                    | Seminal parameters (sperm concentration, motility, morphology) | Significant improvement in Group 1 compared to Group 2 |
|                 |      | controlled study | Clomiphene citrate/Vitamin A + Vitamin E + selenium/L-carnitine/pentoxifylline/antioxidants | 107   | 12 months           | Pregnancy rate                       | 47.1% in Group 1 versus 21.5% in Group 2   |

RCT: randomized controlled trial; *abstract only

**Antioxidants**

Antioxidants are commonly used as adjuvant therapy after surgical management of varicocele. Parados Galatito et al.24 conducted a randomized controlled trial involving 42 patients who had undergone retrograde embolisation for clinical varicocele and persisted with oligozoospermia 6 months after surgery. Twenty patients were allocated in the treatment arm receiving antioxidant therapy (including N-acetyl cysteine 600 mg per day with vitamins and minerals) for 3 months while 22 patients were included in the control arm receiving placebo. At the end of 3 months, the sperm count in the treatment arm significantly improved from 14 to 32 million ml−1 (P = 0.009) while no significant improvement occurred in the control arm. No statistical difference in progressive motility (P = 0.752) and typical forms (P = 0.926) were found. Further analysis suggested a 20 times higher chance of improving sperm counts after antioxidant therapy compared to controls. However, this improvement did not translate into a higher pregnancy rate when the patients were followed up for 12 months after cessation of therapy.

Zinc and folic acid are also used as adjuvant therapies.26-28 Takihara et al.26 treated 65 infertile men with or without varicocele with zinc therapy (440 mg daily) and 36 infertile men postsurgical varicocelectomy with similar zinc adjuvant therapy for a variable period of 2 months to 2 years. The postvaricocelectomy group showed significant improvement in sperm motility (P < 0.05) at 2 months and 12 months of therapy. Twenty-eight percentage of men who received only zinc therapy impregnated their wives compared with 50% of the postvaricocelectomy group. Zinc was thus concluded to play some role in improvement in seminal parameters postvaricocelectomy. Azizollahi et al.27 randomized 102 infertile patients after varicocelectomy used to repair clinical grade 3 varicocele into four groups such as 32 receiving zinc sulfate 66 mg per day alone, 26 receiving folic acid (5 mg per day) alone, 29 receiving combination therapy, and 25 receiving placebo for 6 months starting immediately after surgery. There was mild improvement in control arm. Patients receiving zinc sulfate therapy showed significant improvement in only sperm morphology (percentage of normal sperms increased from 40% to 53%, P < 0.05) while those receiving folic acid showed significant improvement only in sperm concentration (27 million ml−1 to 49 million ml−1, P < 0.05). Patients receiving combination therapy showed significantly improved sperm concentration (30 million ml−1 to 47 million ml−1, P < 0.05), morphology (percentage normal sperm increased from 46% to 57%, P < 0.05), and motility (percentage of sperm with forward progressive motility increased from 28.7% to 43.0%, P < 0.05) at the end of 6-month treatment. Further analysis on hormonal parameters and seminal plasma biomarkers showed significant increase in blood Inhibin B levels (from 127.9 to 190.1 pg ml−1, P < 0.05) after combination therapy.
Seminal superoxide dismutase (SOD) activity showed significant improvement in groups receiving zinc therapy alone (63.3% to 71.4%, \( P < 0.05 \)) and combination therapy (58.8% to 68.4%, \( P < 0.05 \)) for 6 months. No significant change in nitrous oxide concentration and total antioxidant capacity of seminal plasma was noted. In conclusion, zinc and folic acid combination therapy does seem to have a positive impact on seminal parameters after surgery, but its clinical implication in terms of pregnancy outcome is still unclear.

**Chinese medicine**

In 1997, Chen and Liang\(^{29}\) reported the combined role of surgery followed by Chinese medicine in the management of male infertility with varicocele. The authors recorded pregnancy rates as high as 72%. Guo \(^{30}\) compared surgery followed by Chinese medicine with dexamethasone and Vitamin E combined found significantly higher sperm parameters and pregnancy rates with surgery and drug combination than medical therapy alone. Yan \(^{31}\) et al. studied *jingling* oral liquid in a randomized controlled study as an adjuvant therapy after varicocelectomy and compared it with hCG in 60 patients. They reported a significant improvement in seminal parameters, seminal superoxide dismutase and zinc levels and higher pregnancy rate in the Chinese medicine group compared with hCG group.

**Miscellaneous**

Ketotifen, a tricyclic benzocycloheptatriophene, a mast cell stabilizer, is thought to counteract the ability of mast cells to trigger inflammatory response, thereby improving sperm quality. Azadi \(^{32}\) et al. randomized 103 patients with clinical varicocele and infertility subjected to varicocelectomy to two groups such as 51 patients received ketotifen 2 mg per day for 3 months and 52 patients received no drug. Assessment of seminal parameters 3 months after surgery revealed marked improvement in seminal parameters in both groups, the treatment group (\( P < 0.01 \)) and control group (\( P < 0.05 \)). On comparing the seminal parameters between the two groups, there was no significant difference in sperm density (\( P = 0.95 \)), sperm morphology (\( P = 0.1 \)) before surgery. Three months after surgery, the treatment group which received adjuvant ketotifen showed marked improvement in sperm density (\( P = 0.004 \)) and sperm morphology (\( P = 0.001 \)) compared to control group. The impact on sperm motility was not significant. On follow-up of these groups for 9 months, pregnancy rate was significantly higher in the group which received adjuvant ketotifen (41% vs 21%, \( P < 0.05 \)).

**DISCUSSION**

Similar to the problem with empirical drug therapy for idiopathic male infertility, empirical drug therapy for varicocele-associated infertility suffers from a lack of well-conducted studies that could offer high levels of evidence.\(^{33}\) The problem stems from an unclear target of therapy, poorly designed studies, small numbers, varying drug combinations, and inadequate outcome measures. In the absence of live birth data, surrogates such as change in oxidative stress levels, sperm parameter improvements, and even pregnancy rates are insufficient evidence to support prescriptions. Some of the studies reviewed in this article have shown sperm parameter improvement rates with placebo to be as high as 38%–46%.\(^{34}\) In view of such data, unless large prospective trials are conducted, most such therapies will remain empirical.

A number of studies reviewed in this manuscript provide a "proof of concept" or rationale for medical therapy to men with varicocele but fall short of providing true evidence. This is particularly true for antioxidants which are associated with a lack of harm and, therefore, seem to be the best candidates for both research and clinical use.
Since there is high-level evidence to suggest that in the appropriate patient, varicocelectomy results in improvement of outcomes, treating infertile men with a varicocele with drugs alone cannot be recommended. However, success after surgical intervention for varicocelectomy is not universal. Many such men will have persistent oligoasthenoteratozoospermia and will fall into the category of idiopathic seminal abnormalities since the identifiable surgical cause, namely the varicocele, has already been corrected. They are thus candidates for empirical treatment similar to their counterparts who never had a surgically correctable cause. Antioxidants are the most commonly prescribed drugs in this patient population both due to theoretical benefits, preclinical studies, and lack of significant harm. This may be a group where empirical drug therapy, primarily with antioxidants, plays a role.

CONCLUSIONS
Current evidence cannot support recommendation of medical therapy alone to infertile males with abnormal seminal parameters and clinically palpable varicocele. Surgery remains the treatment of choice. Since surgery for varicoceles does not always result in success, adjunctive therapy after surgery may be an acceptable option. Adjunctive therapy with antioxidants may provide additional benefit. Research using valid end-points such as pregnancy is required before these therapies can become a standard treatment option.

AUTHOR CONTRIBUTIONS
HG is responsible for data acquisition, manuscript first draft, manuscript critical revision, and approval of final draft; RK is responsible concept design, data acquisition, manuscript critical revision, approval of final draft, and overall supervision.

COMPETING INTEREST
The authors declared no competing interests.

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