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Review Article

EFFECT OF ASPIRIN ON REPRODUCTIVE PROFILE OF MALE RAT AN-OVERVIEW

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ABSTRACT

Aspirin (Acetylsalicylic acid) is widely used in human and veterinary as anti-inflammatory, cardiovascular prophylaxis, anti-clotting agent and to decrease cancer risk. However, it is often mis- or over-consumed, including in population subgroups, such as elite athletes, to prevent pain and treat injuries. Many risks associated with its usage have been reported but there is a deficiency of information about its affects on androgenic studies, histology of the testes, kidneys, livers and reproductions. In this paper we tried to collect the information about it deleterious toxicity effects on male rat reproduction. The literature findings showed that Aspirin deadly affect the production of sperm and reproductive hormones; in-addition decreases the testicular weight and also affect the blood profile. Effect of aspirin on the male reproductive system may be due to being a Prostaglandins inhibitor. While hepatic and renal toxicity further reveal aspirin deleterious toxic nature.

Keywords: Aspirin, Toxicity, male rat, Spermatogenesis, Haematology.

INTRODUCTION

Aspirin (Acetylsalicylic acid) was introduced to treating human more than 100 years ago [1] due to its anti-inflammatory and anti-pyretic benefits it is widely used in clinical settings. First of all it was reported by [2] that aspirin and non-steroidal anti-inflammatory drugs inhibit the synthesis of pro-inflammatory prostaglandin E2. later on was reported that aspirin has inhibitory effects on cyclooxygenase-1 (COX-1) activity by acetylating serine 530 [3] and COX-2 [4].

Aspirin has been reported effected response to decrease the risk of cancer [5] and heart problems [6] due to its anti-thrombotic action [7] which is due to its inhibition of the cyclooxygenase (COX) enzyme that metabolizes arachidonic acid to a variety of prostanoids, including thromboxane A2 [8]. The anti-platelet effects of aspirin has been tested in various forms of coronary artery disease, pregnancy-induced hypertension and preeclampsia in angiotensin-sensitive primigravida at low dosage and showed positive results in most of the reports [9]. Today Aspirin is one of the most widely used analgesics available without prescription in several parts of the world, according to estimation 4000 tonnes of it is used every year [10].

Recent year's literatures create a lot of awareness and realization of the genotoxic ability of drugs, food additives, and environmental pollutants [11]. It has been reported that aspirin has many adverse effects like long term use of it causes gastrointestinal [12], stomach problem and cerebral problems [13]. Intracerebral and subarachnoid hemorrhages are the most serious risks associated with the use of aspirin [14]. The increased incidences of infertility in male due to frequent use of a number of therapeutic drugs, has made efforts to study their untoward side effects on the male reproduction. Various drugs used for treating diseases are reported to cause male infertility, Infertility is a major problem for 15-20% of young couples [15] and about 50% of infertility is related to problems in male [16]. One of very worse effect of aspirin is on reproduction of male. Sperm production is the main reproductive activity of male fertility, and it is affected by many different factors like therapeutic and non-therapeutic agents such as chemicals and radiation and environmental factors are able to regulate or affect

sperm production [17]. It has been reported that aspirin treated rat showed a significant decrease in the testicular weight [18], decreased activities of sorbitol dehydrogenase, hyaluronidase [19], decreased number of spermatids and increased spermatocytes nuclei were observed [20]. The process of spermatogenesis and the accessory reproductive organs function are dependent on androgen activity. Aspirin administration to normal rats resulted in hypercholesterolemia that's might be due to decreased androgen production, resulted accumulation of cholesterol in testes [21]. The impaired sperm dynamics, including spermatogenesis, could be an outcome of aspirin-induced alteration in cholesterol metabolism in testis [22].

Normal reproduction depends on the androgenic activity of animal. Aspirin can decrease the androgenic activity in rats which leads towards decreased hormones production which are most crucial components for normal reproductive activity in males.

Effect on testicular weight

The seminiferous tubules and contents are the primary contributor to testicular weight. The process of spermatogenesis occurs in the seminiferous tubules of the testis and within the seminiferous tubules, testosterone is the major androgen present [23]. Either a decreased length of seminiferous tubules or a decreased density of elements within a given length including decreased density due to degeneration of spermatogenic elements would affect testes weight and decreased length of Seminiferous tubules implies either fewer spermatogonial stem cells or a lower mitotic activity of these stem cells [24]. It was reported by Vyas at al. [25] that aspirin treated group had decreased testicular volume as compared to control group. Aspirin also produced a significant decrease in Leydig cell nuclear volume in comparison to that of the controls, decrease in the weight and nuclear volume of the Leydig cell might be conducted through indirect involvement of inhibition of androgens biosynthesis [26]. It is well understood that weight, size, and secretary function of reproductive parts like testes, epididymis and seminal vesicles are closely regulated by androgens hormones [27].

Testis weight are correlated with fertility because larger testicular weight have been associated with an increase in daily sperm production, daily sperm output, Sertoli cell numbers and smaller testis is associated with poorer fertility due to less number of sperm production [28]. Decreased testicular weight means decreased length of seminiferous tubules which are the primary site for spermatogenesis, resulted decreased reproductive activity.

On other hand, it is also have been reported that aspirin treated rats group body weight was not significantly altered which is sign that aspirin is not toxic to the animals as well as non-androgenic in nature, since androgens are known to posses anabolic activities like stimulating the development and growth of the skeleton and skeletal muscles [29].

Effect on sperm dynamic

In a germ cell's path to make a spermatozoon from a spermatogonium, a spermatogonium divides by mitosis in the basal compartment, of the seminiferous tubules, to produce either stem cells or committed spermatogonia that ultimately become primary spermatocytes. These cells pass through the blood-testis barrier of the Sertoli cell tight junctions as they move into adluminal compartment. They continue their development in the immunologic-protected site of the adluminal compartment and produce sperm [30].

Male fertility is affected by number of factors including anatomical abnormalities like ductal obstructions, varicocele, or ejaculatory disorders, however, a big portion (40-90%) of cases are believed to be caused by deficient sperm production [31]. It was reported by [19] that aspirin treated rat had highly significant decreased in the total number of sperm including decreased sperm motility, effectiveness and increased in the percentages of dead sperm. Damage to the sperm cell by substances may occur by one of three mechanisms: physiological, cytotoxic and genetic morphological abnormalities might have been caused by alterations in testicular DNA that in turn disrupts the process of differentiation of spermatozoa [32] exposure to chemicals that could produce pituitary-hypothalamic effects which in turn could affect spermatogenesis exposure of the seminal fluid to chemicals, resulting in functional or structural impairment of sperm cells [33]. The effects of aspirin on the total number, motility, and effectiveness of the sperm are the most important factors affecting fertility as because increase the number of dead sperm to half of the total leads to complete infertility [34]. Spermatogenesis is regulated by androgenic activity [26], while hypercholesterolemia have been diagnosed in aspirin treated rats testes [35] which is a sign of decreased androgen production, leads to impaired

spermatogenesis [36]. The ability of aspirin to affect the motility is the sign that aspirin was able to permeate the blood-testis barrier with a resultant alteration in the microenvironment of the inner part of the wall of the Seminiferous tubules [29]. Decreased hyperactivation of sperm in aspirin treated animal can be due to its impact on the flow of calcium into sperm which is necessary for the formation, activation, and movement of sperm [37] or might be due to its uncoupled oxidative phosphorylation and COX inhibiting activity pathway [38].

Reproductive toxicant affects sperm motility indirectly through disruption of epididymis epithelial cell function or might be by acting directly the spermatozoa by affecting their enzymes [39]. So it can also be assumed that might be aspirin caused toxicity, in-turned decreased reproductive profile in male rats.

Aspirin not only decreases the numbers of sperm and its motility but also including to it damage of sperm morphology which is might be due to interference of aspirin in spermatogenesis process or due to interaction of testosterone on hypothalamic release factor which can cause changes in spermatogenesis [40]. The increased percentage of sperm damaged morphology is an indication of the increase in the rate of induced mutations on the sperm cells at the level of spermatogenesis. Aspirin-induced reduction in sperm dynamics might be an outcome of depressed levels of androgens thereby affecting physiological maturation of the sperm resulting in reduced sperm count, motility, and density [36]. Mohammed [41] Explained that giving aspirin to adult mice cause a decrease in the activity of certain enzymes such as Hyaluronidase, which is secreted by sperm and contributes to the process of ovarian Penetrate rubble during the process of fertilization. Decreased activity of hyaluronidase, decreased number of spermatids and increased size of spermatocytes nuclei is the sign that aspirin cause impairment on later stage of spermatogenesis.

Effect on hormones production

Testosterone is the principle male sex hormones in mammals, birds and other vertebrates, it is produced in the Leydig cells within the testes [42]. Primary action of testosterone is anabolic growth, spermatogenesis promotion and promotion of secretion from the accessory sex glands. Mild analgesics like aspirin have recently been incriminated by several epidemiological and toxicological studies to act as endocrine disruptors [43]. Aspirin treated rat had decreased level of testosterone production [44].

This has been reported that aspirin treated group had decreased Sertoli cells number and changed microscopic appearance, Sertoli cells showed pyknosis and nuclear shrinkage [45]. Interestingly, testosterone receptor (androgen receptor) are present on Leydig cells, Peritubular cells and Sertoli cells but in germ cells of the mature testis don't have any receptor [46] that's why testosterone don't target germ cell directly, instated of that testosterone target the Sertoli cell and these Sertoli cell nourish the germ cell to differentiate in spermatozoa [47]. This could be the possible mechanism of aspirin to interfere the testosterone production by decreasing androgen receptors sites. Adult mammalian spermatogenesis is a testosterone-dependent process, and many studies have shown that testosterone withdrawal from the rat testis results in increased germ cell apoptosis [48] which lead to decreased reproductive ability.

Testosterone levels in the adult testis of rat should be likely stable and high because germ cell development does not progress beyond the pachytene stage of meiosis if its level is unstable or low [49]. Testosterone is the maintenance and reforming of the blood-testis barrier, which provides a specialized environment for the development of the germ cells and prevents immunogenic germ cell antigens from reaching the immune system [50]. As a Whole decreased testosterone production will lead to decreased spermatogenesis as because this hormone is important in the initiation and maintenance of spermatogenesis.

Other possible reason for decreased testosterone production can be due to decreased luteinizing hormones (LH) production in treated rat. When LH binds to the Leydig cells, it stimulates the cellular messenger cAMP to activate protein kinase A. Protein kinase A undergoes a series of phosphorylations that in turn activate a series of enzymes that synthesis testosterone from the cholesterol base molecule [51]. Which is perhaps due to effect of aspirin on the efficiency of the male reproductive system to work as a disincentive mechanism to configure Prostaglandins in members attached to the gonads, from the other hands its effect on the secretion of the gonads feeders and then secretion testosterone hormone as the same mechanism [52].

Testosterone is not only need for production of sperm it is also required to release of sperm, In the absence of testosterone, mature sperm are phagocytized by the Sertoli cells [53]. Testosterone plays an important role in increasing

the Fertilization portability of sperm *in vivo* and *in vitro* [54].

Collectively, these findings explain the inhibitory effect of aspirin on serum testosterone, and decreased testosterone production will lead to decreased reproductive activity and capacity of male rat.

Histopathological observations

Testis is composed of seminiferous tubules and interstitial tissues. Seminiferous tubules are the site for spermatogenesis and they contain three types of cells: male germ cells, Sertoli cells, and Myoid cells, while Leydig cell are locate between neighbouring seminiferous tubules [55]. According to developmental progression at the base of the seminiferous tubules have spermatogonia, spermatocytes in the middle, and spermatids near the apex of the Seminiferous epithelium [30]. The aspirin treated rats showed cytological and nuclear degenerative changes in seminiferous leading to shrinkage to seminiferous tubules [56] resulted reduction in number of Sertoli cell, Leydig cell, primary spermatogonia, secondary spermatogonia, spermatocytes. These observations suggest degenerative and retrogressive effects of aspirin upon the testes in rats.

In seminiferous tubules Sertoli cells are the most important cell as because germ cell proliferation depend on it, it provides the nutrition to growing germ cell including to it Sertoli cells are involved in the release of spermatids into the seminiferous tubules lumen [57] blood testes barrier, regulating the testicular vasculature [58]. Decreased Sertoli cell number will lead to decreased number of germ cell as their crucial role in nourishment of germ cell and maintain a micro environment which is important for normal growth [59].

Ablating of Sertoli cells, germ cells, seminiferous tubules and Leydig cells resulted reduced testicular size [60]. *In vitro* and *in vivo* studies showed that aspirin in high dose caused death of blood vessel tissue [61]. Aspirin inhibit continuous production of prostaglandin which cause unopposed constriction of arterioles resulting ischemia of tubules and cause epithelial cell death [62]. Decreased testicular vasculature leads to a reduction in fluid exchange between the vasculature and testicular interstitial, which reduces gonadotropins-stimulated circulating testosterone concentrations, indicative of reduced Leydig cell stimulation and/or reduced secretion of testosterone into the vasculature leading to infertility. The present literature finding suggested that the administration of aspirin in rats induces pathological changes in the testes.

Serum and hematological study

Blood is a complex two-phase fluid, made up of plasma and formed elements. The formed elements consist of RBCs or erythrocytes, white blood cells (WBCs or leukocytes) and platelets. The primary function of RBCs is the transportation and delivery of oxygen to the peripheral tissues. However, their mechanical and flow properties are responsible for the complex fluid dynamics which occur in micro vessels [63]. As a corollary, altered biomechanical properties of RBCs can result in impaired oxygen and nutrient supply to peripheral tissues [64].

According to research finding aspirin did not show any significant effect on production of RBCs, but on other hand aspirin treated group had decreased Leukocytes production [19]. Primary role of Leukocytes is in inflammation and immune system [65], Decrease number of Leukocytes suggests that immune and phagocytic function of body have been compromised [66]. Aspirin treated rats had significant reductions in packed cell volume (PCV) and haemoglobin (Hb) values [25] so it could indicate induction of anaemia and decrease in oxygen- carrying capacity of the blood as well as the amount of oxygen delivered to the tissues [67]. Including to all this also have been reported that sub-chronic aspirin treatment in both low-dose and in low-followed-by-higher dose significantly potentiated the glucose lowering effect [68]. Lowering the immunity and glucose leads to reduced reproductive activity as suboptimal glucose level lowers the energy status and reproduction depends on the energy status of animal.

According to finding of Vyas et al. [25] Aspirin treated rat had altered serum biochemistry and the most obvious was increased activities of glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT) in-addition increased level of creatinine and urea. Increased activities f SGOT and SGPT is the sign of hepatic injury [69]. Which reflects that aspirin have toxic effects which might be resulted due to NSAIDs induced inhibition of prostaglandin synthesis which leads to renal vasoconstriction and decreased renal perfusion which is responsible for acute renal abnormalities [70]. Increased level of SGOT and SGPT not only compromise the cellular defence against attack by reactive molecules but also may have profound effects on normal hepatocellular function. Liver is the major target organ for drug metabolism and liver toxicity could be an

outcome of idiosyncratic metabolic reaction where toxic metabolites in hepatocytes binds to cell proteins and leads to abnormalities [71]. According to literature finding of aspirin effects on hepatic and renal profiles further reveal toxic nature of the aspirin when administered to rats.

CONCLUSION

Aspirin is worldwide extensively used medicine both in human and veterinary side. But Aspirin toxicity has deleterious effect on the blood chemistry and reproductive efficiency of Male. So, it is recommended that caution should be exercised in the use of aspirin.

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