



LITERATURE REVIEW

Alternative Uses of Non-Steroidal Anti-Inflammatory Drugs

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are typically indicated for management of pain and fever, relieving inflammation and for prevention of blood clots formation. Aspirin, and particularly low dose aspirin (LDA), has potential therapeutic role beyond the well established indications including the prevention of several diseases such as myocardial infarction, strokes, atherothrombotic events and pulmonary embolism. Many studies have been conducted in recent years in order to recognize these additional potential benefits. These benefits include the management of patent ductus arteriosus (PDA), reduction in pregnancy complications such as preeclampsia and antiphospholipid syndrome (APS), and even certain cancers such as colorectal cancer. This paper will highlight some of the alternative uses and benefits of NSAIDs.

Methods

Using the search engine PubMed, and clinicaltrial.com, we searched the database using the key words "alternate uses of NSAIDs." We also searched for "alternate uses" using individual drug names such as Aspirin, Ibuprofen and Naproxen. These articles and reports were then thoroughly reviewed and relevant therapeutic uses were summarized in this review article.

Patent Ductus Arteriosus (PDA)

Patent ductus arteriosus (PDA) is relatively common in finding among extremely premature infants and has been associated with increased morbidity and

mortality. PDAs are managed medically with NSAIDs, most commonly being Indomethacin and ibuprofen [1]. In a meta-analysis published in JAMA 2018 including 68 randomized trials with over 4,800 infants, a high dose of intravenous ibuprofen was associated with a statistically significant higher likelihood of hemodynamically significant PDA closure versus standard doses of intravenous ibuprofen [2].

In an Early Human Development article published in 2015, infants of less than 28 weeks of gestational age with PDA were treated with indomethacin and ibuprofen. Both drugs showed similar effectiveness and safety profiles [1].

Ohlsson A conducted a systematic review published in 2019 comparing the prophylactic use of ibuprofen compared to placebo or no intervention to decrease the incidence of PDA. It was concluded that prophylactic treatment with ibuprofen should be avoided for prevention of PDA as the prophylactic dose of ibuprofen was associated with considerable side effects including oliguria, worsening serum creatinine levels, and increased risk of gastrointestinal hemorrhage. In addition, the authors also concluded that a new approach to PDA management is an early targeted treatment based on echocardiographic criteria within the first 72 hours of life, that has a higher sensitivity for diagnosing a PDA that is unlikely to close spontaneously. Multiple similar trials are currently ongoing which will include updates about "Ibuprofen for treatment of PDA" [3].



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Preeclampsia

Preeclampsia is one of the known pregnancy complications and currently it is acceptable to prescribe low dose aspirin to pregnant women who are at high risk of preeclampsia. Aspirin is one of the most frequently used drugs in medicine. It belongs to the class of NSAIDs with a wide range of pharmacological activities, including analgesic, antipyretic, and antiplatelet properties.

Obstetric Antiphospholipid Syndrome (APS)

Obstetric Antiphospholipid syndrome (APS) is another known condition associated with pregnancy in which a low dose of aspirin is recommended. The most recognized mechanism of action of aspirin is to inhibit the synthesis of prostaglandins but this by itself does not explain all the ways of anti-inflammatory effects of aspirin. The use of LDA to prevent pregnancy complications such as preeclampsia and obstetric APS has been based on the restoration of the prostacyclin/thromboxane-A2 balance to the dominance of the former. This action is due to aspirin's property to inhibit an enzyme named Cyclooxygenase (COX). However, in the light of newly identified mechanisms of action of aspirin, anti-inflammatory, antioxidant effects and other immunomodulatory effects need to be explored in regard to disease control [4].

Another mechanism to explain the therapeutic effect is the induction of the production of aspirin-triggered lipoxins (ATLs) from arachidonic acid by acetylation of the enzyme cyclooxygenase-2. Availability of stable analogs of ATLs have stimulated further clinical investigations. It has been found that similar to endogenous ATL, synthetic ATLs have similar antiinflammatory, antioxidant and immunomodulatory effects. It is speculated that the underlying antiinflammatory effect of aspirin due to stimulation of ATL formation is reason for its effectiveness in the PE and in the obstetric APS [4].

However, the prescription of these drugs must be particularly careful to minimize the risk in both mother and fetus. Even though aspirin is not exempt of risks, the risk-benefit balance is directed in favor of the beneficial effects.

In another review article published in *Obstetric Anesthesiology* in 2013, the authors documented that use of LDA prior to 16 weeks of gestations results in significant reduction of risk of pre-eclampsia, however, this effect was not observed after the 16 weeks gestation. The incidence of severe preeclampsia, intrauterine growth restriction, or preterm birth was also significantly lower among those women who began LDA before 16 weeks. LDA in combination with low-dose heparin is recommended for treatment of recurrent spontaneous abortion in women with antiphospholipid antibodies [5].

Premature Labor

Premature labor is another known pregnancy complication where NSAIDs have a probable beneficial role in prevention. Prostaglandin inhibitors such as indomethacin have a potent inhibitory effect on uterine contractions, and indomethacin has been used since the 1970s as a tocolytic to delay and treat premature delivery. A meta-analysis conducted by Bloor, et al. concluded that compared with placebo and other tocolytics such as β -sympathomimetic drugs or magnesium sulphate, indomethacin reduces the risk of preterm birth before 37 weeks and causes fewer maternal side effects. However, as with other tocolytic drugs, no clear improvement in neonatal morbidity or mortality has been demonstrated. Furthermore, administration in the second trimester is associated with considerable risk of congenital cryptorchidism. COX-2 inhibitors such as rofecoxib; sulindac, ketorolac, and nimesulide are also effective tocolytic drugs, and it was expected that COX-2 inhibitors might have fewer adverse effects than indomethacin. However, similar complications including oligohydramnios and ductal constriction, has been documented after exposure to the COX-2 specific NSAIDs [5].

In the third trimester, NSAIDs and aspirin are usually avoided because of significant fetal risks such as renal injury, oligohydramnios, constriction of the ductus arteriosus (with potential for persistent pulmonary hypertension in the newborn), necrotizing enterocolitis, and intracranial hemorrhage [5].

Antiphospholipid Syndrome (APS)

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder associated with arterial, venous, or microvascular thrombosis and/or pregnancy complications mainly in young age. In a study reported in *Thieme E-Journals* in 2020, the authors reported that in patients with prior arterial thrombosis, vitamin K antagonists with or without low-dose aspirin are preferred treatment of choice. The authors also suggested that aspirin can be given as a primary prevention in asymptomatic patients with positive antiphospholipid antibodies without thrombosis or pregnancy complications, especially when additional vascular risk factors are present [6].

Chemo-Preventive Effect

In a 2002 article published in the *Biochem J.*, it states that recent studies have shown the possible use of COX-2 inhibitors as chemopreventive agents. In one of these studies, an in vitro array has demonstrated this anti-tumour activity with the ability of these molecules to induce apoptosis in cancer cells. All together, these findings have led the U.S. Food and Drug Administration to approve of celecoxib (Celebrex), a COX-2 inhibitor, as an adjuvant treatment of familial adenomatous

polyposis. In addition, celecoxib has been successfully tested in numerous advanced clinical trials against a variety of epithelial malignancies including colon, esophagus, skin and bladder cancers [7].

The risk of formation of adenoma in the colon among frequent NSAID users was 26.8% versus 39.9% among placebo subjects who later used NSAIDs sporadically. Aspirin has also shown to reduce the incidence of colon adenomas and mortality, especially when used for > 10 years. Rofecoxib, while associated with the reduction of colorectal cancer, was associated with increased cardiovascular risk. Adenoma Prevention with Celecoxib trial shows that, for patients of all genotypes, the estimated cumulative incidence of one or more adenomas by year 3 was 59.8% for those randomized to placebo as compared with 43.3% for those randomized to low-dose (200 mg, twice daily) celecoxib (relative risk [RR] = 0.68; 95% CI = 0.59-0.79; P < 0.001) and 36.8% for those randomized to high-dose (400 mg, twice daily) celecoxib and 60.7% in placebo group (RR = 0.54; 95% CI = 0.46-0.64; P < 0.001). Celecoxib was also found to increase the radio sensitization of colon cancer cells [8].

Both preclinical and clinical studies have demonstrated promising results of the role of celecoxib in the treatment and prevention of cancer and the best outcome was observed in colon, breast, prostate and head and neck cancers. However, more clinical trials providing real evidence-based clinical advances of celecoxib use are needed [9].

Another prospective study exhibit mitigation in prostate cancer in young male group by inhibiting by cyclooxygenase pathway [10].

NSAID Reduced the Incidence of Parkinson Disease

Parkinson disease or paralytic agitans is progressive degenerative disease. In a systemic review conducted by Gagne, et al, it was recommended that use of NSAID reduced the incidence of PD by inhibiting the neuroinflammatory activity. The result showed a 15% reduction in risk of PD on non-aspirin NSAID use compared to aspirin use beside with protective effect on long-term use. To control the bias in the study, the confounding factors like smoking, age, caffeine intake, alcohol and gout were well controlled [11]. In 2009 Sami, et al., published another meta-analysis of 11 studies regarding the NSAID on PD. They observed the duration of NSAID was long term (6 years) and ibuprofen had a protective effect from RR 0.76 to 0.79, and CI 95% 0.65 to 0.69 on PD compared to other NSAIDs [12].

Cancer Related Anorexia/Cachexia Syndrome (CACS)

In advanced stages of cancer, tumors cell releases cytokines and TNF which triggers C-reactive protein level, lipolysis, protein breakdown along with decreased

intake leading to weight loss and shortening the quality of life.

DC Macmillan in 1999 reported a 12-week Prospective randomized trial on gastrointestinal cancer with weight loss studying the use of megestrol acetate and placebo compare to megestrol acetate and ibuprofen. From baseline to the end of study (12 weeks) both groups showed significant improvement in appetite but the megestrol acetate and placebo had weight loss (-2.8 kg) compare to the group of megestrol acetate and ibuprofen weight gain (+ 2.3 kg) with significant decline in C-reactive protein level, which resulted in improvement in the quality of life and increase survival rate. However, this study was performed on small groups with confounding factors and side effects related to the NSAID. To fully elaborated the beneficial effect of megestrol acetate and ibuprofen uses in weight gain, it was suggested to conduct a large database meta-analysis with other type of cancers [13].

Actinic Keratosis

Sun exposure causes excessive UV light radiation that leads to proliferation of keratinocytes, which trailed to actinic keratosis and can progress to squamous cell carcinoma in future.

Aditya K Gupta in 2012 reported a systematic review on tropical use of multiple agents along with the use of diclofenac to perceive the improvement in actinic keratosis and the result revealed that tropical use of diclofenac was as effective as 5-fluorouracil, imiquimod and laser treatment [14].

Apoptotic activity of NSAID is well-known and acts via Cox-1 and Cox-2 dependent and independent inhibitor pathways. Katrin singer, et al. in 2019 comprehensively elaborated the diclofenac use in actinic keratosis with significant improvement in clinical outcomes [15,16].

Conclusions

To the best of my knowledge, we found that the above-mentioned conditions are the ones where the alternate benefits of NSAIDs have been reported in literature so far apart from their well-known analgesic, antipyretic and anti-inflammatory effects. Amongst these benefits include the management of PDA, reduction in pregnancy complications such as preeclampsia and APS, and certain cancers such as colorectal cancer, Parkinson disease, weight gain in cancer subjects and actinic keratosis.

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