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Comparison of intra-articular injection of Naproxen and glutathione in treatment of knee rheumatoid arthritis in a male rabbit model

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Rheumatoid arthritis (RA) is a chronic progressive inflammatory joint disorder. Targeting drug delivery spares adverse effects and optimizes therapy. This study sought to compare the hematological and immunological impacts of intra-articular Naproxen sodium and glutathione (GSH) in an arthritis rabbit model. Twelve adult male rabbits (2.5–3.5 kg weight), were placed in separate cages under standard conditions and divided into 4 groups (3 each). The positive control group (PCG) was given intra-articular (IA) bovine serum albumin (BSA), the negative control group (NCG) was given IA normal saline, the GSH group was given IA BSA with GSH for three days, and the Naproxen group was given IA BSA with Naproxen for three days. Blood samples were collected from the lateral saphenous vein and marginal ear vein at day seven post treatment with BSA into plain tubes to separate serum for the rheumatoid factor (RF) test. The second collection of blood fraction was used for blood indices, including RBCs (red blood cells), Hb (hemoglobin), HCT (hematocrit), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), RDWCV (red cell distribution width – coefficient of variation). The Naproxen group showed the highest RBCs (6.4 ± 0.2), Hb (14.2 ± 0.4), and MCHC (33.6 ± 0.5), while also demonstrating elevated MCH (22.3 ± 0.6) and maintaining HCT levels (42.1 ± 1.0). The GSH group demonstrated the lowest levels of these parameters. Regarding WBCs, the GSH group showed the highest value in WBCs (10.5 ± 1.64), compared to the positive control ($P = 0.003$), negative control ($P = 0.021$), and Naproxen groups ($P < 0.001$). The Naproxen group demonstrated the lowest total WBC count (5.7 ± 1.0) and markedly reduced lymphocyte percentage (55.9 ± 6.1) compared to all other treatment groups. The PLT count revealed marked variations in the four treatment groups, with the positive control group demonstrating significantly lower PLT versus all other groups. The positive control group reported significantly elevated RF (24.0 ± 13.5) levels compared to other treatment groups ($P < 0.001$ for negative control and glutathione, $P = 0.002$ for Naproxen). The results confirmed significant improvement in WBC count in the glutathione group compared to the Naproxen group. This study concluded that an intra-articular glutathione injection may alleviate arthritis. Yet, further investigation is required to better understand the role of glutathione role in the healing course of arthritis.

Keywords: rheumatoid arthritis; intra-articular injection; glutathione; Naproxen.

Introduction

Rheumatoid arthritis (RA) is a common chronic inflammatory disorder (Matloob et al., 2024), with a global prevalence rate of approximately 1%, and imposing extensive socioeconomic burdens on healthcare systems (Finckh et al., 2022). Patients present with permanent synovial inflammation, contineous joint damage, and systemic symptoms. RA mainly affects synovial joints, with the knee joint being the most affected site (Conran et al., 2023).

The pathophysiology of RA involves a complex interaction of inflammation and oxidative stress (Kaur et al., 2021). Pro-inflammatory cytokines involved mainly include tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which directs the inflammatory reaction leading to synovial hyperplasia, cartilage degradation, and bone erosion (Pretorius et al., 2017). Moreover, the oxidative stress directs RA progression, leading to excessive formation of reactive oxygen species (ROS) and exhaustion of antioxidant system leading to tissue damage and propagation of the immune response (Zamudio-Cuevas et al., 2022).

Available treatment approaches for RA include a spectrum of interventions, varying from disease-modifying antirheumatic drugs (DMARDs) to biological agents and synthetic DMARDs (Smolen et al., 2020; Prasad et al., 2023). Nonetheless, systemic use of these drugs often presents limitations, including suboptimal drug concentrations at target sites, systemic side effects, and distinct therapeutic responses (Donahue et al., 2008; Khanna et al., 2021; Brown et al., 2024). Therefore, intra-articular injection seems an attractive approach, providing direct drug delivery to the joint involved, while minising systemic exposure and concurrent side effects (Evans, 2005; Butoescu et al., 2009; Jones et al., 2019). For pain relief, a non-steroidal anti-inflammatory drug (NSAID)is given, most commonly Naproxen, with anti-inflammatory activity (Parolini, 2020). Recently, glutathione has been administered to tackle oxidative stress, providing an adjuvant therapeutic role in the treatment of RA (Fonseca et al., 2019; Bilski & Nuszkiewicz, 2025).

For patients living with RA, the daily joint inflammation is most often treated with oral therapy which travels through the entire body en route to the inflamed joints, with unwanted side effects in the non-target areas. With this in mind, it is worth considering intra-articular injection to protect the body organs from unwanted side effects. The present study was designed to investigate the efficacy and hematological deficit associated with Naproxen and glutathione using a rabbit model for RA.

Materials and methods

Twelve adult White New Zealand male rabbits have been used weighing 2.5–3.5 kg. The animals were obtained from animal house in the College of Veterinary Medicine, University of Mosul, Mosul, Iraq. The rabbits were placed in separate cages at a room temperature of about 25 ± 2 ºC. Food and water provided ad libitum. After two week of acclimatization, the animals were randomly divided into four groups (3 animals each) according to the following regimen:

– Group 1: animals injected with BSA intra-articular in the knee joint to induce rheumatoid arthritis at dose of 10 mg/mL (positive control) for three days;

– Group 2: animals injected with normal saline 1 mL intra-articular in the knee joint (negative control) for three days;

– Group 3: animals injected with BSA intra-articular in the knee joint to induce rheumatoid arthritis then treated with glutathione using a 30 °G needle at dose 20 mg/kg for three days;

– Group 4: animals injected with BSA intra-articular in the knee joint to induce rheumatoid arthritis then treated with Naproxen using a 30 °G needle at dose 100 mg/kg for three days.

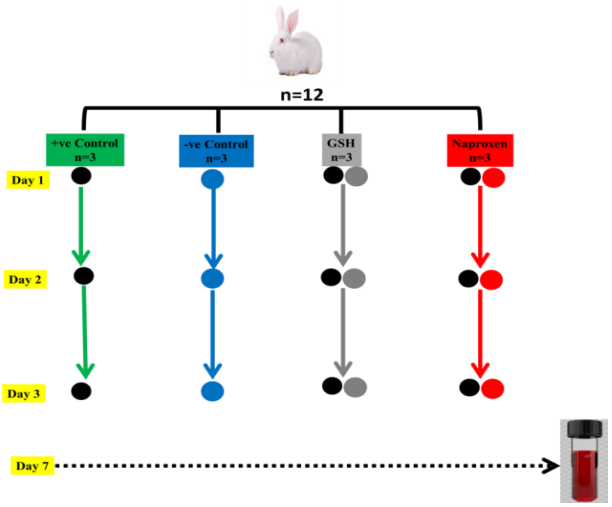

Fig. 1. Study design of the positive, negative control, and experimental rabbits used in the present research: black circle – BSA, blue circle – normal saline, grey circle – GSH (glutathione), red circle – Naproxen

Blood samples were collected from lateral saphenous vein and marginal ear vein at day seven post treatment with BSA into plain tubes to separate serum for the rheumatoid factor (RF) test.

The second collection of blood was taken at day 7 post treatment with glutathione and Naproxen in EDTA tubes and in plain tubes for a complete blood picture (CBC) and RF test. The rabbits were euthanized according to the guide lines of the ACUC.

The CBC was performed using a CBC analyzer (Genotek, USA) while the RF Test was performed using an RF kit (BioSystems, Spain).

The experiment was conducted according to the guidelines and approval of the Animal Care and Use Committee (ACUC) of Alnoor University College (ALN.U.C/AUP-R0002, Mosul, Iraq).

Results were stated as mean and standard deviation (mean ± SD). The data were analyzed using ANOVA (one-way analysis of variance) and performed by Minitab18 program and SigmaPlot 12.5. Tukey's test was used as a method to relate the significance level between the groups. Significance level was accepted at probability value of $P \leq 0.05$.

Results

The hematological results revealed distinct findings over the four groups, the Naproxen group showed the highest RBCs (6.4 ± 0.2), Hb (14.2 ± 0.4), and MCHC (33.6 ± 0.5), while it also demonstrated elevated MCH (22.3 ± 0.6) and maintained HCT levels (42.1 ± 1.0). Conversely, the GSH group demonstrated the lowest levels of these parameters including RBC (5.8 ± 0.1), Hb (12.7 ± 0.4), and HCT (39.3 ± 1.0). Nonetheless, this group still revealed the highest MCV (67.4 ± 1.3). The negative control group showed intermediate to high values, particularly excelling in HCT (42.5 ± 1.4) and RDWCV (14.2 ± 0.6), while the positive control group demonstrated moderate parameters with the lowest MCV (65.2 ± 0.8) and RDWCV (13.5 ± 0.1, Table 1).

Table 1
The hematological parameters in the rabbits treated with Naproxen versus glutathione

Parameters	Positive control group	Negative control group	Glutathione group	Naproxen group
RBC, 10^6/µL	6.1 ± 0.2^{ab}	6.3 ± 0.1^{a}	5.8 ± 0.1^{b}	6.4 ± 0.2^{a}
Hb, g/dL	13.1 ± 0.2^{b}	13.8 ± 0.3^{a}	12.7 ± 0.4^{b}	14.2 ± 0.4^{a}
HCT, %	39.5 ± 0.5^{b}	42.5 ± 1.4^{a}	39.3 ± 1.0^{b}	42.1 ± 1.0^{a}
MCV, fL	65.2 ± 0.8^{b}	67.3 ± 1.2^{a}	67.4 ± 1.3^{a}	66.1 ± 0.9^{ab}
MCH, pg	21.4 ± 0.3^{b}	21.8 ± 0.2^{ab}	21.9 ± 0.6^{ab}	22.3 ± 0.6^{a}
MCHC, g/dL	32.9 ± 0.1^{c}	32.3 ± 0.3^{b}	32.3 ± 0.4^{b}	33.6 ± 0.5^{a}
RDWCV, %	13.5 ± 0.1^{b}	14.2 ± 0.6^{a}	13.9 ± 0.1^{ab}	13.8 ± 0.3^{ab}

Note: the data expressed as mean and standard deviation for each group; different letters indicate significant differences at P value less than 0.05 using ANOVA with posthoc Tukey test; GSH – glutathione, RBC – red blood cells, Hb – hemoglobin, HCT – hematocrit, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RDWCV – red cell distribution width – coefficient of variation.

The WBCs results revealed variations between the four treatment groups. The GSH group showed the highest value for WBCs (10.5 ± 1.6), compared to the positive control ($P = 0.003$), negative control ($P = 0.021$), and Naproxen group ($P < 0.001$). MON levels (17.2 ± 1.5) were markedly elevated in the GSH group compared to the positive control group, alongside reduced GRAN (13.5 ± 2.8) compared to both negative control and Naproxen group. The Naproxen group demonstrated the lowest total WBC count (5.7 ± 1.0) and markedly reduced lymphocyte percentage (55.9 ± 6.1) compared to all other treatment groups. This lymphocyte suppression was significant compared to positive control ($P = 0.008$), negative control ($P = 0.011$), and glutathione groups ($P = 0.002$). The negative control demonstrated slight elevation in WBC (8.4 ± 0.8) and the lymphocyte percentages in both control groups were in the upper 60s range (Table 2).

Table 2
Leukocytes in the rabbits treated with Naproxen versus glutathione

Parameters	Positive control group	Negative control group	Glutathione group	Naproxen group
WBC	7.5±0.54c	8.4±0.78c	10.5±1.64a	5.7±0.95b
LYM	67.8±2.37b	68.08±3.9a	69.1±4.26a	55.9±6.08ab
MON	14.5±2.5b	16.5±0.73a	17.2±1.46a	15.95±0.47b
GRAN	17.8±1.02a	15.45±3.39a	13.48±2.83b	17.9±0.3a

Note: data expressed as mean and standard deviation for each group; different letters indicate significant differences at P-value less than 0.05 using ANOVA with posthoc Tukey test; WBC – white blood cells, LYM – lymphocytes, MON – monocytes, GRAN – granulocytes.

The platelets count revealed marked variations in the four treatment groups, with the positive control group demonstrating significantly lower platelet level, at 424.8 ± 47.6, than all other groups. The negative control group demonstrated the highest platelet level at 666.8 ± 94.6, and the level in the Naproxen group was 640.3 ± 58.4 and in the glutathione group 604.5 ± 48.0 (Table 3).

Table 3
The platelet counts in the rabbits treated with Naproxen versus glutathione

Parameter	Positive control group	Negative control group	Glutathione group	Naproxen group
PLT	424.8 ± 47.6^{b}	666.8 ± 94.6^{a}	604.5 ± 48.0^{a}	640.3 ± 58.4^{a}

Note: data expressed as mean and standard deviation for each group; different letters indicate significant differences at P-value less than 0.05 using ANOVA with posthoc Tukey test; PLT – platelets.

The positive control group reported significantly elevated rheumatoid factor (24.0 ± 13.5) levels compared to the other treatment groups ($P < 0.001$ for negative control and glutathione, $P = 0.002$ for Naproxen). The negative control and glutathione groups demonstrated a non-detectable rheumatoid factor (0.00 ± 0.00, Table 4).

Table 4
The serum rheumatoid factor
in the rabbits treated with Naproxen versus glutathione

Parameter	Positive control group	Negative control group	Glutathione group	Naproxen group
RF	24.0 ± 13.5^{a}	1.00 ± 0.001^{b}	0.001 ± 0.001^{b}	5.75 ± 0.48^{c}

Note: data expressed as mean and standard deviation for each group; different letters indicate significant differences at P-value less than 0.05 using ANOVA with posthoc Tukey test; RF – rheumatoid factor.

Discussion

The Naproxen group demonstrated the most positive hematological parameters, including superior RBCs counts, Hb concentrations, and MCHC values that exceeded those of both control and GSH groups. A study conducted by Ogidi et al. (2020) confirmed similar hematological alteration by different NSAIDs, with marked reductions in PCV, RBCs, and Hb in different treatment groups, reflecting the fact that these drugs induce subclinical anemia. Interestingly, some NSAIDs (Indomethacin, Celecoxib, Aspirin, and Diclofenac) demonstrated increased Hb levels, via boosted bone marrow activity or enhanced heme biosynthesis (Ogidi et al., 2020). Similarly, in a study by Darwish & Eldakroury (2020), the administration of Dipyrone, and Meloxicam to sheep caused transient macrocytic hypochromic anemia at day 3 after therapy, confirmed by reductions in RBC count, Hb, PCV, MCH, and MCHC.

Conversely, Ibuprofen reduced RBC count with concurrent reduction MCHC in a fish model, with paradoxical increase in Hb, HCT, MCV, and MCH, which has been explained by the argument that fish are trying to compensate for the reduced RBCs by increasing Hb to meet the tissue oxygen demands. Moreover, Ibuprofen increased MCV and MCH in fish due to increased release of immature reticulocytes in an attempt to compensate for tissue anemia stress (Saravanan et al., 2012). Moreover, low doses of Diclofenac administered to fish resulted in increased RBC and HCT, suggesting that Diclofenac may initially promote compensatory erythropoiesis or cause hemoconcentration as an adaptive mechanism. Conversely, high doses of Diclofenac resulted in decreased Hb with normal RBC and HCT levels. This could be explained in the light that Diclofenac at high dose may interrupt Hb degradation leading to hypochromic anemia. Nevetheless, in either doses the MCV, MCH, and MCHC were unchanged, suggesting that the stability of these parameters is related to the fact that Diclofenac does not necessarily alter the size or Hb content per cell, and hence these changes in total Hb are more likely due to altered synthesis rates rather than changes in cellular morphology or maturation patterns (Ribas et al., 2015). Testing the impacts of Flunixin, Metacam and Carprofen on the blood indices revealed mild suppression of RBCs, Hb, and HCT in all treated group, hence triggering reticulocytosis (Dobre et al., 2019).

This enhancement in RBC indices suggests that Naproxen may have unanticipated effects on erythropoiesis and RBC maturation (Parolini, 2020). The glutathione treatment was associated with the lowest RBC counts, Hb concentrations, and HCT values compared to other groups. These results confirmed that glutathione antioxidant results in erythropoiesis and plays a role in preserving RBC's membrane integrity and cellular function. However, elevated MCV observed in this group suggests possible alterations in RBC shape or developmental deficits. Perhaps this could potentially related to the antioxidant protection provided by glutathione (Bilski & Nuszkiewicz, 2025).

In the GSH group WBC increased compared to the positive or negative control groups or the Naproxen group, reflecting the fact that GSH triggered immune system stimulation. GSH has selectively increased MON and LYM levels alongside reduced GRAN. In contrast, Naproxen treatment induced a reduction in WBC counts, which aligns with Naproxen's mechanism of inhibition of COX enzymes and subsequent reduction of inflammatory markers release. The different NSAIDs have distinictive impacts on WBC counts – with marked reduction in the Piroxicam, Celecoxib, and Aspirin groups, but increases in the Diclofenac, Ibuprofen, and Indomethacin groups – suggesting distinctive mechanisms of hematological toxicity that may be associated with hematopoietic deficits (Ogidi et al., 2020). Moreover, Gomaa (2018) demonstrated complex immune responses to NSAID, the maintenance of total WBC counts despite alteration in the WBCs' subpopulation in all tested NSAIDs (Diclofenac, Ibuprofen, and Paracetamol), indicating that NSAIDs induced alteration in distinictive lineages rather than complete bone marrow suppression (Gomaa, 2018). In the study by Darwish & Eldakroury (2020), the administration of Dipyrone, and Meloxicam to sheep demonstrated alterations in blood indices, they caused leukocytopenia and neutropenia at day 3 after commencing therapy, suggesting a suppressive effect on granulopoiesis, possibly mediated through cytokine inhibition or direct toxic effects on myeloid cells (Darwish & Eldakroury, 2020). Ibuprofen increased WBC count in fish, presumably in an attempt to protect against the Ibuprofen pharmaceutical toxicant, which was continued during the exposure period (Saravanan et al., 2012). Low and high doses of Diclofenac resulted in decreased WBC levels, perhaps resulting in interference with innate immune and adaptive immune responses (Ribas et al., 2015). Testing the impacts of Flunixin, Metacam and Carprofen on the WBC revealed neutrophilia with relative lymphocytopenia in all treated group, hence triggering direct immunomodulatory effects (Dobre et al., 2019).

Compared to the positive control group, both Naproxen and GSH preserved PLT, which suggests that neither treatment intervention adversely affects platelet homeostasis. Naproxen affects PLT function rather than PLT number, indicating preserved megakaryocyte activity and thrombopoiesis despite cyclooxygenase inhibition. The antioxidant properties of glutathione may contribute to enhanced platelet survival by protecting these cells from oxidative damage during circulation. Ketoprofen has induced marked thrombocytopenia, through Ketoprofen-induced lactic dehydrogenase inhibition in platelets (Razi et al., 2014). Ibuprofen has shown suppression of platelets (De La Cruz et al., 2010). Moreover, Mannava et al., (2019) found that one week of treatment with Naproxen reduced the PLT concentration in the leukocyte-rich platelet-rich plasma samples. In a systematic review, it has been concluded that patients treated with Ibuprofen or Indomethacin demonstrated decreased PLT aggregation but no change in PLT count and similarly, treatment with Meloxicam caused a non-significant change in PLT count (Kao et al., 2022).

The results confirmed undetectable RF levels in the GSH group and reduction in the Naproxen group, reflecting the suppression of immune response and effective restoration of immune homeostasis to baseline values. This could be explained by the possibility that GSH may perpetuate the oxidative stress cascades that perpetuate autoimmune inflammation. Moreover, GSH directly suppresses the production of RF via suppression of plasma cells due to redox-regulating inflammatory signaling pathways, including NF-κB and AP-1 (Rahman, 2000). The incomplete RF suppression noticed in the Naproxen group, reflecting important but incomplete immune suppression, suggests that while Naproxen reduces inflammatory activity, residual immune processes remain active (Ceuppens et al., 1986; Cicala et al., 2000). This could be explained in the context of Naproxen's mechanism of action of blocking prostaglandin synthesis and interrupting inflammatory cascades, highlighting the fact that alternative pathways continue to drive immune reactions (Saper et al., 2012; Bashir et al., 2024). In contrast, GSH provided a wider immune response suppression at multiple levels due to redox-sensitive transcription factors, reflecting the superior nature of GSH anti-inflammatory effects (Lei et al., 2015; Diotallevi et al., 2017; Silvagno et al., 2020).

Conclusion

This study concluded that intra-articular Naproxen versus glutathione has shown distinct blood indices in the rheumatoid arthritis model. Naproxen demonstrated superior blood indices and superior immunosuppressive effects, while GSH demonstrated lower blood indices and superior WBC. However, both treated groups maintained normal PLT counts and demonstrated complete suppression of rheumatoid factor levels. These findings indicate that Naproxen offers

anti-inflammatory effects, while glutathione offers a more balanced immune response.

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The authors declare that there is no, conflict of interest.

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