The Effect of Honey and Uncaria on The Prevention of Post Laparotomy Intraperitoneal Adhesions in Rats

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number and the volume of IPA. The data observed were analyzed by one way ANOVA with level of significant P<0.05. Result: IPA occurred in all animals of study group I and III (6/6), but it was much less in the group II (2/6). The number of IPA formed in group I (1.33±0.52) and group III (1.33±0.52) were significantly (P<0.05) greater than group II (0.33±0.52). The volume of IPA in group I (0.23±0.24 ml) and group II (0.09±0.15 ml) were statistically (P<0.05) less than group III (0.61±0.43 ml). Conclusion: The present study demonstrated that honey could reduce the incidence, the number and the volume of IPA, while uncaria appears enhancing the volume of IPA.

Keywords: intraperitoneal adhesions, post laparotomy, honey, uncaria

INTRODUCTION

Intraperitoneal adhesions (IPA) might occur in patient post laparotomy (67-93%) and post pelvic surgery (97%) 1,2, that could increased morbidity and mortality 3,4. IPA are the major causes of intestinal obstruction and secondary infertility. IPA is fibrous tissue that connected to abdomen wall with various organs in cavum abdomen (ex. intestine, utery, etc.) 5.

Abstrak: Latar Belakang: Adhesi intraperitoneum pasca laparotomi (AIP) selalu diikuti dengan peningkatan morbidity dan mortalitas. Anti inflamasi non-steroid telah digunakan untuk mencegah terjadinya AIP. Madu dan uncaria (gambir) secara turun temurun telah digunakan sebagai obat anti radang. Penelitian ini bertujuan untuk melihat efek madu dan uncaria pada pembentukan AIP pada tikus. Metoda: 18 ekor tikus Sprague Dawley (berat badan: 150-200 gram) dibagi dalam 3 kelompok (n=6), yaitu: (I) Kelompok kontrol 1 cc aquadest sebagai placebo, (II) madu (1 g/kgbb), dan (III) uncaria (10 mg/kgbb). Masing-masing kelompok diberi obat 2 kali sehari selama 3 hari segera setelah dilaparotomi. Pada hari ke-10, masing-masing tikus dibunuh untuk dilakukan laparotomi ulang dan selanjutnya melihat adanya kejadian, jumlah dan volume AIP. Data dianalisis dengan menggunakan ANOVA, dimana suatu perbedaan dinyatakan bermakna, bila P<0,05. Hasil: AIP didapati pada seluruh hewan percobaan kelompok I dan III (6/6), dan kelompok III kejadiannya lebih sedikit (2/6). Rerata jumlah AIP pada kelompok I (1,33 ± 0,52) dan kelompok III (1,33 ± 0,52), lebih banyak (P<0,05) dibanding dengan kelompok II (0,33 ± 0,52). Volume AIP pada kelompok I (0,23 ± 0,24 ml) dan kelompok II (0,09 ± 0,15 ml) lebih sedikit (P<0,05) lebih sedikit dibanding kelompok III (0,61±0,43 ml).

Kesimpulan: Penelitian ini menunjukkan bahwa madu dapat mengurangi kejadian, jumlah dan volume dari AIP, sebaliknya uncaria tampaknya meningkatkan volume AIP.

Kata kunci: adhesi intraperitoneum, pasca laparotomi, madu, uncaria
In order to prevent postoperative IPA, many adjuvants have been used in animal models and in the clinical trials. Non steroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin production, have been shown to decrease adhesion formation. The formation of IPA can be prevented after administering NSAIDs, i.e.: nimesulide, diclofenac, meloxicam, ketorolac, and celecoxib.

Traditional medicines which have anti-inflammatory action such as temulawak (Curcuma xanthorrhiza) and sambiloto (Andrographis paniculata) have been demonstrated to be able preventing the formation of IPA. Honey and uncaria are other traditional agents that have been studied and used as anti inflammatory agents. In the present study, we investigated the effect of honey and uncaria on the formation of IPA in rat.

**MATERIALS AND METHODS**

Eighteen Sprague Dawley rats, weighing 150–200 g, were used in the present study. All rats were observed for several days to ascertain their health before study conducted. All procedures were approved by the Animal Care and Use Committee of the Universitas Sumatera Utara.

Before surgery, rats were randomly assigned into three groups (n=6), i.e. group I control group received 1 cc aquadest as placebo, group II received honey (1 g/kgbw), and group III received uncaria (10 mg/kgbw). All rats recovered without incident after surgery and resumed preoperative physical activity and feeding patterns postoperatively. Each drug was orally administered twice daily for three consecutive days post laparotomy. Under an ether anesthesia, the abdomen was shaved and prepared with a povidone iodine solution. Using sterile technique, a 5 cm vertical midline incision was done. Care was taken to avoid gross bleeding from injured sites. Handling of other tissues was minimized. The incision was closed in a single layer, excluding the peritoneum, with a running 3–0 monofilament delayed absorbable suture and interrupted suture to skin. The total operative time was less than 10 min. On day 10, each rat was killed by deep general anesthesia and then re-laparotomy with vertical paramedial incision.

The data observed (i.e. the incidence, the number and the volume of IPA) were analyzed by one-way ANOVA with the level of significance was set at $P < 0.05$.

**RESULTS**

During the study period there was no one of rats died. We found that the incidence IPA occurred in all animals of study group I and III (6/6), but it was much less in the group II (2/6) (Figure I).

The average of number of IPA formed in group I receiving aquadest as placebo (1.33±0.52) and group III receiving uncaria (1.33±0.52) were significantly ($P<0.05$) greater than group II receiving honey (0.33±0.52) (Figure II).

The volume of IPA in group I (0.23±0.24 ml) and group II (0.09±0.15 ml) were statistically ($P<0.05$) less than group III (0.61±0.43 ml) (Figure III).

**DISCUSSION**

To the best of our knowledge, this is the first study conducted to demonstrated the prevention of postoperative IPA by traditionally agents honey and uncaria.
An inflammation is the initial response to peritoneal injury that leads to extravasations of serum and cellular elements. The site of peritoneal injury is covered predominantly by polymorphonuclear cells entangled in fibrin strands, which are soon outnumbered by macrophages. When normal fibrinolysis occurs, islands of mesothelial cells proliferate throughout the injury site and completely cover the defect within 4–5 days. It was therefore in the present study the drugs treated administered for 3 days only. It has been found that various inflammatory mediators such as prostaglandins (PGF\textsubscript{2} and PGE\textsubscript{2}) might play an important role in the process of adhesion formation\textsuperscript{18,19}. Ibuprofen the inhibitor of prostaglandin formation appeared to significantly inhibit the formation of adhesions as compared with that in untreated control animals\textsuperscript{7}.

During peritoneal repair, the cellular events appear to be coordinated at least in part by cytokines. The antibodies to IL-6\textsuperscript{20}, tumour necrosis factor-\alpha (TNF-\alpha) and interleukin-1 (IL-1)\textsuperscript{21} reduce postoperative adhesion formation. It has been demonstrated that COX-2 expression is highly induced by a number of cytokines, including IL-1, TNF-\alpha, and other stimuli associated with inflammation and growth\textsuperscript{22}. Nimesulide at therapeutic concentrations is a potent inhibitor of IL-6 production\textsuperscript{23}. Inhibitor effect of nimesulide on TNF-\alpha production may also contribute to its anti-inflammatory properties.

In this study, it was demonstrated a significant reduction in postoperative IPA formations in rats treated with honey administration, but uncaria appears enhancing the volume of IPA. How come uncaria appears to enhance IPA?

Pane et al. (2007) demonstrated that celecoxib an selective COX-2 inhibitor has different effect on the formation of IPA. Compared to the low dose of celecoxib (1.4 mg/kgbw), the high dose of celecoxib (7 mg/kgbw) may enhance the incidence (5/5; 100% vs 0/5; 0%), the number (1,40±0.55 vs 0,20±0.45), and the volume of IPA (0,53±0.22 ml vs 0,06±0.13 ml).

It was reported previously that high dose celecoxib will stimulate the activity of NF-kB\textsuperscript{24}, which may then stimulate TNF-. It means the high dose of celecoxib has no anti-inflammatory action but has an antioxidant action. It appears that uncaria has similar action as occurred with celecoxib.

The antioxidant and anti-inflammatory effects of uncaria have been assessed in vitro. Uncaria has potency for inhibiting tumor necrosis factor-alpha (TNF-alpha) synthesis; this cytokine is a key mediator of chronic inflammatory processes such as arthritis. An important finding was that TNF-alpha production was effectively suppressed at much lower concentrations of uncaria than were needed to produce antioxidant effects. Previous research has shown that TNF-alpha is a worthwhile therapeutic target, but it is not known whether the beneficial effects of uncaria are due to TNF-alpha inhibition alone. In addition, prostaglandin E2 production was significantly reduced by uncaria, suggesting that cyclooxygenase-2 expression was inhibited\textsuperscript{26}.

In summary, based on the experimental results, it is suggested that honey could reduce the incidence of IPA, while uncaria enhancing the volume of IPA. Findings should be evaluated further in other experimental animal models and human trials.

REFERENCES


