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Recirculating chemohyperthermia as a treatment for non-muscle invasive bladder cancer: Current and future perspectives

Javier Flores-Carbajal, Alejandro Sousa-Escandón, Daniel Sousa-Gonzalez, Silvia Rodriguez Gomez, Manuel Lopez Saavedra, M Elia Fernandez Martinez

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Abstract

About 75% of all bladder cancer diagnosed are non-

muscle invasive bladder cancer (NMIBC), recurring over 50% of them after transurethral resection of the bladder tumor. In order to prevent recurrences, adjuvant intravesical chemotherapy with mitomycin C and immunotherapy with bacillus Calmette-Guérin (BCG) is traditionally used. Unfortunately, many patients relapse after receiving these treatments and a significant proportion of them require surgery. After a one-to-three years BCG maintenance, the risk for progression at 5 years was 19.3% for T1G3 tumors. Many new treatment approaches are being investigated to increase the effectiveness of adjuvant intravesical therapy. One of the developing treatments for intermediate and high-risk NMIBC is the combination of intravesical chemotherapy and hyperthermia, called chemohyperthermia. This article provides a review of the mechanism of action, current status and indications, results and future perspectives.

Key words: Bladder cancer; Thermo-therapy; Non-muscle invasive; Chemohyperthermia; Recirculating; Intravesical chemotherapy; Treatment; Mechanism of action

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Core tip: Chemohyperthermia has demonstrated a selective cytotoxicity on tumoral cells without affecting the remaining healthy cells and it significantly increases the penetration of MMC during intravesical instillations. Moreover, hyperthermia and many chemotherapeutic agents have a synergistic effect, significantly reducing the relative risk of tumoral recurrence in patients non-muscle invasive bladder cancer. Recirculative systems are a novel way to apply endovesical chemohyperthermia, which achieves excellent clinical results with a better side effects profile and a lower price than the one of other chemohyperthermia technologies.

Flores-Carbajal J, Sousa-Escandón A, Sousa-Gonzalez D, Rodriguez Gomez S, Lopez Saavedra M, Fernandez Martinez ME. Recirculating chemohyperthermia as a treatment for non-muscle invasive bladder cancer: Current and future perspectives. *World J Clin Urol* 2017; 6(2): 34-39 Available from: URL: <http://www.wjgnet.com/2219-2816/full/6/i2/34.htm> DOI: <http://dx.doi.org/10.5410/wjcu.v6.i2.34>

INTRODUCTION

Bladder cancer is the fourth tumor with the highest incidence in men, after lung, prostate and colorectal cancers. About 75% of all bladder cancer diagnosed are non-muscle invasive bladder cancer (NMIBC), recurring over 50% of them after TURBT^[1].

In order to prevent recurrences, adjuvant intravesical chemotherapy with MMC and immunotherapy with bacillus Calmette-Guérin (BCG) is traditionally used. Intravesical chemotherapy, with single postoperative or with maintenance protocols, is the common treatment for patients with low and intermediate NMIBC risk^[2]. Immunotherapy with BCG is the gold standard treatment for high-risk patients. However, BCG is associated with important side effects as systemic tuberculosis and bladder retraction^[3]. Unfortunately, many patients relapse after receiving these treatments and a significant proportion of patients require surgery, therefore, 19% of those patients with T1G bladder cancer, after adjuvant treatment with BCG (1-3 years), progressed after 5 years^[4].

Considering the high relapse and progression after the adjuvant treatment, treatment alternatives have been investigated in order to improve the intravesical treatment outcomes. For those patients with intermediate and high NMIBC risk, the combination of intravesical therapy with hyperthermia (CHT) has been developed.

To write this paper, we reviewed all major database available on internet (MEDLINE, EMBASE, Cochrane Library, Web of science and ClinicalTrials.gov) including both clinical trials as general reviews.

HYPERTHERMIA

Also called thermotherapy, is a type of therapy for tumors in which the whole body, or part thereof, is subjected to high temperatures (up to 45 °C). Numerous studies have shown that high temperatures damage and kill cancer cells by preventing the denaturing of their proteins and the DNA repair. However, hyperthermia causes little damage to normal tissue^[5,6]. The first clinical experiences in the use of hyperthermia as a treatment for cancer were performed by Coley^[7] more than a century ago. Hyperthermia may be applied in different ways, such as a whole body, regional, intracavitary, local, or interstitial hyperthermia. Similarly, sources of heat vary and include microwaves, ultrasound, radiofrequency and recirculating

liquid systems.

In bladder tumors, there are two types. One is used in infiltrating cancers and involves the application of external heat on the entire pelvis associating radio or chemotherapy^[8] while the other is used in NMIBC, consisting in the intravesical application of heat (through microwaves or recirculation of heated liquids). In this type of treatment, a chemotherapeutic agent is associated to the heat in order to achieve a synergistic effect by using both treatments together which are known as CHT^[9].

MECHANISM OF ACTION OF HYPERTHERMIA

The human body has several autonomic mechanisms of regulating body temperature to ranges suitable for normal functioning^[10].

Cellular necrosis and apoptosis occurs at a temperature above 40.5 °C and cell, molecular and metabolic disorders, also known as HT effect, contribute to this fact^[11].

The effect of heat on both normal body cell function and on cancerous cells varies based on the degree of hyperthermia with different cytotoxic, vascular and immune effects (Table 1).

MMC AND HEAT

MMC absorption increases with high temperatures. The absorption thereof is significantly affected by dilution, urinary pH and exposure time. They observed that, with passive instillations, the absorption of the administered dose is less than 30%^[12].

In 2001, Paroni *et al.*^[13] showed that microwave-induced hyperthermia increased considerably the MMC absorption, after 30, 45 and 60 min ($P < 0.008$). It is important to understand that the MMC absorption increase is not only due to increased permeability of the bladder urothelium, but also to a noteworthy increase in solubility. Therefore, while at 25 °C, the maximum concentration that can get by dissolving 1 g of MMC is 0.8 mg/mL, this value is doubled at 40 °C since concentrations are up to 1.7 mg/mL (Data from Kyowa Hakko Kirin Co Ltd.).

It stems from the above that the chemohyperthermia (CHT) is the combination of intravesical chemotherapy and hyperthermia in order to increase efficiency. In summary, the increased cell permeability, the changes in the blood perfusion, and the direct cytotoxic effect, are the reasons why the MMC efficacy increases when it is combined with heat^[13,14].

CHEMOHYPERTHERMIA

There are two types of treatment: Adjuvant (intermediate and high-risk NMIBC) and neoadjuvant. To improve the effectivity of intravesical chemotherapy are

Table 1 Mechanisms of action of hyperthermia

	39-41	41-43	43-45
Direct Cytotoxic Effects	Slight growth arrest	Reversible growth arrest Mainly in phase M and S Brief RNA synthesis impaired Prolonged DNA synthesis impaired	Irreversible growth arrest Permanent protein denaturalization DNA repair impaired Activation of both ways of apoptosis
Immune effects	Initial increase of intracellular HSP followed by increase of extracellular HSP Signals to immune cells Cross-priming of CD8 ⁺ T cells Dendritic cell activation Natural Killer activation Increase cytosine release (IL-6, IL-10)	As above	Altered cytosine production Inactivation of immune cells Reduced expression of extracellular HSP
Vascular effects	Vasodilatation which means: Improved tumor blood flow Improve tissue O ₂ Reduce acidosis Improve drug absorption	Improved tumor blood flow: Improve tumor oxygenation Improve drug delivery	Reduced tumor blood flow due to vascular collapse Microthrombosis Endothelial cell damage Vessel permeation Increased acidosis and reduce tissue O ₂

Adapted from Rampersaud *et al*^[11]. IL: Interleukin.

used “device assisted”, these are fundamentally two: Electromotive drug administration (EMDA) that enhance the absorption of MMC by using iontophoresis. On the other hand, it is the chemohyperthermia (CHT) the one that is based on heating the bladder with the instilled chemotherapeutic drug.

EMDA, CHT and device assisted

EMDA uses an electric current to enhance transepithelial drug penetration. EMDA is administered *via* a battery-powered generator delivering an electric current of 0-30 mA DC at 0-55 V, which is passed between two electrodes: An active electrode is placed into the bladder as part of a transurethral catheter and the dispersive ground electrode pads are placed on the skin of the lower abdomen. EMDA takes advantage of three phenomena: Iontophoresis, electro-osmosis and electroporation. Iontophoresis involves propelling a substance into tissues by passing an electrical current through a solution containing the charged active ingredient^[15].

The first CHT system approved for human use was the Synergo™ System. This system has been used for 15 years and has conclusive studies in both neoadjuvant and adjuvant settings. It has proved clinical efficacy in high-risk patients (including BCG failures and CIS). It has demonstrated a 60% reduction of tumoral recurrences when comparing to standard MMC. Moreover, its better results were maintained during time periods up to 10 years.

An alternative way to apply heat to the bladder are those systems based on recirculation of a solution of chemotherapeutic drugs heated externally and reintroduced to the bladder through a triple lumen catheter. Two different devices using this technology are currently available: Combat BRST™ and BWT™ systems, which are based on simple technology, and use cheap disposables that make it attractive for performing CHT

in a sustainable public medicine. They both use a triple lumen modified Foley catheter, which are soft and flexible, avoiding most problems related to the urethral catheterization, which appear with other technologies. They both enable the removal of the MMC from the patient in safe disposals without contact to the sanitary staff. They both try to maintain the chemotherapeutic solution at a fixed temperature but there are some differences between them. Main differences about all three devices may be seen in Table 2.

Adjuvant CHT treatment

As described above, most patients with high-risk bladder cancer recur one year after the TURBT^[16]. This justifies the study of adjuvant treatment strategies. Colombo *et al*^[17] performed a multicenter, prospective and randomized study comparing CHT with MMC and MMC alone, in 42 and 41 patients respectively, as adjuvant treatment after the TURBT. The recurrence rate in the CHT and MMC group was 17.1% vs 57% in the other group. The meta-analysis performed by Lammers *et al*^[18] found a 59% decrease in recurrences after combined therapy (CHT with MMC) and only 10.6% of patients ended up on radical cystectomy.

In our center^[19], there was a recurrence free disease rate of 87.5% in high-risk patients treated with Combat recirculant CHT and to whom a 2-year follow-up was performed. However, Ekin *et al*^[20] showed that the recurrence rates of high-risk patients treated with BWT recirculant CHT were 82% and 61% after 1 and 2 years of follow-up.

The first randomized trial comparing CHT vs BCG was published by Arends *et al*^[16]. They observed a recurrence-free survival after 2 years of follow-up of 78% in the CHT group vs 64.8% with BCG ($P < 0.0082$). Progressions were lower than 2% in both groups ($P = NS$). In another study, the therapy has not been shown to be as effective as the BCG, although this is a

Table 2 Characteristic of devices for intravesical chemohyperthermia treatment

Device	Synergo™	BWT system™	Combat™
Heat Source	Intravesical 915 MHz microwave antenna (Recirculating cooling system)	External heating plates (Recirculating heating system)	External flat, low volume heat exchanger (Recirculating heating system)
Temperature and fluctuation	40 °C-44 °C ± 3 °C	45 °C	43.5 °C ± 1 °C
Priming volume	± 100 mL	± 50 mL	± 30 mL
Catheter characteristics	20 Fr. Rigid (Radiofrequency emitter + cooling system inside)	18 Fr Flexible	16 Fr Flexible
Advantages	Strong supporting evidence (<i>neoadjuvant and adjuvant</i>) Long term follow up Proved superior to BCG Proved effectiveness against CIS	Simple and Cheap	Lower dilution of MMC Proved effectiveness in sequential schedules Proved neoadjuvant effectiveness Medium term follow up Simple and Cheap
Disadvantages	Higher side effects Lower patient tolerance Intravesical Hot and cold spots Expensive device and disposables Continuous machine control required while working	Limited evidence Quick and Turbulent flow + higher temperature (increase hematuria and reduce patient tolerance)	Limited evidence (multicentric studies ongoing)

BCG: Bacillus Calmette-Guérin.

retrospective study^[21,22].

Some comparative studies between patients who have not responded to treatment with BCG vs non-previously-treated patients showed better results in the former group. The interim analysis of Lombardia project (unpublished data from R. Colombo, Milan-Italy) showed that, after two years of follow-up, the recurrence-free rates of patients treated with *de novo* CHT were significantly better than those who had previous failed intravesical treatment (91% and 62%, respectively $P < 0.006$). In the same vein, van der Heijden *et al*^[23] followed 76 patients treated with CHT during 2 years, observing a 42% recurrence in the group with a previous failed BCG treatment compared to a 24% of recurrences in *de novo* treatment group.

A sequential treatment study by using intravesical BCG and CHT was performed in Leicester United Kingdom to treat 33 high-risk NMIBC patients (including a 40% with Cis) which were followed during a median of 16 mo^[24]. Three of them (9%) did not respond and were proposed for radical cystectomy. Two (6%) showed tumoral progression and were treated with radiotherapy. The other 85% of them were disease-free after follow up.

Neoadjuvant CHT treatment

Colombo *et al*^[25] evaluated the ablative efficacy of neoadjuvant hyperthermia in bladder cancer for the first time in 1998. In that study, 19 patients with NMIBC tumors which were unresectable in a one-stage TURBT in which a cystectomy was indicated, were instead treated with neoadjuvant CHT. After eight doses of hyperthermic MMC per week, a complete TURBT was possible in 16 patients (84%). A histological examination of the specimen showed a tumor absence in 47% (complete response) of the patients and > 50% tumor reduction (partial response) in the other 37%. A cystectomy was

performed on the remaining three patients. After an average follow-up of 33 mo, eight superficial recurrences were resected without having to remove the bladder.

Our group published in 2014 a small series of 15 patients treated with eight weekly doses of recirculating neoadjuvant MMC achieving a 66.6% CR and 33% PR. As in the previous case, the beneficial effect of CHT remained in time and, after 3 years of follow-up, only two patients showed recurrences (15%) which were treated with TUR-B and intravesical adjuvant MMC^[26]. Lüdecke *et al*^[27] reported after TUR-B, 76.1% complete response and 7.6% partial response.

Safety

The CHT Side effects may occur during and after treatment. Arends *et al*^[16] analysed the side effects; during the treatment, the most frequent side effects were bladder spasm in 14%, and bladder pain in 11.4%. After the treatment, the most frequent were the dysuria (11.7%) and the increase of the voiding frequency (9.9%).

With the microwave technology, the most common adverse events during treatment were spasms of the bladder (21.6%) and bladder pain (17.5%). Bladder Spasms tend to occur more frequently with neoadjuvant treatment (17.8% vs 10.7%, $P = 0.398$)^[18]. Similar results were seen with BWTTM^[20,21] and CombatTM^[26,28] recirculant systems. Side effects are frequent but almost all cases were stages 1 and 2.

In our experience, with almost 800 recirculant instillations, only 3.1% of doses were delayed and less than 1% were definitely not performed. The main reasons for delaying were infection, hematuria and irritative chemical cystitis. The only reasons for the anticipated end of the treatment were allergy or intolerance to catheterization. Approximately 6% of the doses were interrupted before the 60 min, usually by bladder spasms or pelvic

discomfort^[26,28]. Those patients who did not tolerate well the first dose, were orally premedicated with 600 mg of Ibuprofen or antispasmodic treatment depending on whether they had complained of pain or spasms. In selected cases spasmolytic IV were administered during treatment. Both oral medications and IV proved to be effective to achieve a good tolerance in subsequent doses of CHT.

FUTURE PERSPECTIVES

The growing interest in magnetic nanoparticles for biomedical applications stems, in part, from their ability to respond to applied magnetic fields through translation, physical particle rotation or internal dipole rotation. As a result, there is local conversion of magnetic field energy into either mechanical forces and/or thermal energy. Then, if magnetic nanoparticles are placed in contact with the desired tumoral tissue, either by intravesical instillation or systemically, and an alternating magnetic field is applied, the heat dissipation due to the nanoparticles will apply a high thermal dose, which will cause the tumoral cell death.

Magnetic fluid hyperthermia is attractive because of the possibility of developing particles whose physicochemical properties are able to attach selectively tumoral tissues through a combination of the enhanced permeation and retention effect^[29-33] and, even better, through the activation through surface ligands^[34]. This could result in the localization of nanoparticles in the extracellular matrix surrounding cancer cells, or in the cellular uptake and accumulation in intracellular structures, such as vesicles, endosomes and lysosomes. But these nanoparticles are not only able to deliver heat near the tumor but also chemotherapies which will develop a synergic effect over tumoral cells^[35,36].

Moreover, nanoparticles joined to chemotherapies are not the only way to increase synergistic effect of CHT. Experimental work performed by Dr. Inman at Duke University, showed that by delivering intravenous novel heat-activated drugs and heating up the bladder, the activated form of the drug could allow the administration of a dose that is 10 to 30 times higher and free-floating drug, while reducing toxicity from other parts of the body (not published data).

Also of growing interest is the use of hyperthermia in combination with immunotherapy treatments. Heating the body activates the immune system, increasing interactions between immune cells designed to alert the body when it is under attack and mobilizing immune cells such as T and B cells to tissues where they are needed^[37,38].

CHT is a concept and a developing technology, which comes to remain, and many of the future strategies against cancer will include this promising therapy.

CONCLUSION

CHT published results in neoadjuvant and adjuvant

therapy are encouraging. It is likely that in the future the CHT is an alternative to BCG and MMC therapy.

Current CHT is an option in BCG refractory tumors. Those who are intolerant to BCG are unsuitable for radical cystectomy or in the context of the international BCG shortage. Their uses instead of MMC, both in adjuvant or neoadjuvant protocols, are promising options pending further evaluation.

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Basic Study

Urinary supersaturation as a diagnostic measure in urolithiasis

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Abstract

AIM

To demonstrate that urinary supersaturation *per se* is not a reliable diagnostic measure of the risk for stone formation.

METHODS

Available physical and chemical data for calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate (brushite, BRU), and urinary supersaturations with respect to COM and BRU in healthy individuals and stone formers, were obtained from the literature. Classical theory of nucleation was used for calculations.

RESULTS

It was found that the rate of homogeneous nucleation (unaided by substrates) of COM and BRU is nil at all conceivable supersaturations of urine. Consequently spontaneous formation of crystals in urine requires the presence of nucleation substrates for (heteronuclei).

CONCLUSION

Urinary supersaturation with respect to lithiatic compounds is a necessary, but not a sufficient condition for nephrolithiasis. The absence of crystallization inhibitors and the presence of efficient nucleation promoters (heteronuclei) in urine are further necessary conditions of urolithiasis occurrence. Urinary supersaturation *per se* is not a reliable diagnostic measure of the risk of kidney stone formation.

Key words: Urinary supersaturation; Heterogeneous

nucleation; Urolithiasis

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Core tip: The supersaturation of urinary compounds has been considered during long time as a key risk factor for renal lithiasis. Nevertheless, theoretical studies demonstrate that the rate of spontaneous (homogeneous) nucleation of calcium oxalate monohydrate and brushite only occurs at urinary supersaturations much higher than conceivable in any individual. This demonstrates the necessity of presence of efficient substances or foreign solid particles for induced nucleation (heterogeneous) of lithiatic compounds. Consequently, urinary supersaturation per se is necessary but not sufficient condition for stone development. Fundamental condition of renal stone formation and development is presence of heteronuclei and significantly reduced content of crystal growth inhibitors. Identification of nucleation promoters and absence of crystal growth inhibitors is very important as a diagnostic aspect to avoid urolithiasis.

Söhnel O, Grases F. Urinary supersaturation as a diagnostic measure in urolithiasis. *World J Clin Urol* 2017; 6(2): 40-43 Available from: URL: <http://www.wjgnet.com/2219-2816/full/6/i2/40.htm> DOI: <http://dx.doi.org/10.5410/wjcu.v6.i2.40>

INTRODUCTION

The supersaturation of urine with respect to lithogenic compounds as a key risk factor for urolithiasis has been introduced by Robertson *et al*^[1]. Rodgers recently showed that urinary supersaturation of calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate (BRU) varied widely among healthy individuals and stone formers and that it was impossible to discriminate between these two groups based on urinary supersaturation levels. Rodgers therefore concluded that urinary supersaturation *per se* is not useful as a diagnostic measure of the risk of stone formation^[2].

The aim of this contribution is to demonstrate that the conclusion of Rodgers is fully substantiated based on the theory of precipitation.

MATERIALS AND METHODS

The driving force for the transfer of one "molecule" of a solute (electrolyte) composed of v ions from solution into the solid phase, ϕ , is the difference of the chemical potentials of the solute in solution and in a macroscopic crystal, $\Delta\mu$, expressed as a positive quantity^[3].

$$\phi = -\Delta\mu = kT \ln (a_{\text{soln}}/a_{\text{cryst}}) \quad (1).$$

where k is the Boltzmann constant (1.38×10^{-23} J/K), T is the absolute temperature (K), a_{soln} is the activity of a solute in solution and a_{cryst} is the activity of a solute in

a macroscopic solid. The activity of a ionic solute $A^{v_A}B^{v_B}$ (electrolyte) is^[2]: $a_{\text{soln,cryst}} = a_{\pm}^v = a_A^{v_A}a_B^{v_B}$ (2).

where a_A and a_B are the activities of ions A and B, v_A and v_B are the stoichiometric coefficients and $v = (v_A + v_B)$ is the number of ions that form "molecule" of solute. The driving force for mass transfer can be expressed as: $\phi = v kT \ln S$ (3).

The supersaturation S is a measure of the thermodynamic driving force for crystallization at a constant temperature (our case) defined as: $S = a_{\pm,\text{soln}}/a_{\pm,\text{cryst}}$ (4).

where a_{\pm} is the mean activity of an electrolyte. The activity of a solute in a macroscopic crystal is equal to the activity of solute in a saturated solution. No mass transfer of solute to solid phase, *i.e.*, crystallization, can proceed if $S = 1$.

The supersaturation of COM) and BRU is defined as: $S = [(a_A a_B)/K_{a,\text{sp}}]^{1/2}$ (5).

where $K_{a,\text{sp}}$ is the respective thermodynamic solubility product. The supersaturation SS used by Rodgers^[2] and the supersaturation S defined by eq. (5) are related by $S = (SS)^{1/2}$.

The classical model of nucleation assumes the formation of a solid phase nucleus in a supersaturated solution by gradual attachment of building units (ions) to the already formed crystalline "cluster" of these units. The rate of homogeneous nucleation, *i.e.*, spontaneous formation of crystalline nuclei in the bulk solution by accretion of ions that is not facilitated by a solid substrate, in 1 m^3 per second can be expressed as^[3]: $J_{\text{hom}} = (2D/d^5) \exp(-\Delta G^*/kT)$ (6).

where D is the diffusion coefficient of the solute ($10^{-9} \text{ m}^2/\text{s}$), d is the molecular diameter, ΔG^* is the change of Gibbs energy accompanying formation of the critical nucleus and k and T are as defined above.

The rate of heterogeneous nucleation, *i.e.*, spontaneous formation of crystalline nuclei facilitated by a solid substrate, in 1 m^3 per second is^[4]: $J_{\text{het}} = (2D/d^5) \exp[-\Delta G^* f(\theta)/kT]$ (7).

The correction factor $f(\theta)$ is smaller than 1 and can be best considered as a measure of the nucleation enhancement by the foreign substrate without ascribing to it any precise physical interpretation. Heterogeneous nucleation occurs at a lower supersaturation than homogeneous nucleation.

The energetic barrier for formation of a nucleus is^[3]: $\Delta G^*/kT = (\beta v^2 \sigma^3)/[(kT)^3(v \ln S)^2]$ (8).

where β is the geometrical factor (32 for a cube), v is the molecular volume, σ is the interfacial tension.

Nuclei smaller than the critical size are unstable and disintegrate, whereas nuclei of the critical size or larger further grow to macroscopic sizes. The number of molecules, N^* , forming the critical nucleus is^[3]: $N^* = 2\beta v^2 \sigma^3/\phi^3$ (9).

RESULTS

COM has a molecular weight of 0.1461 kg/mol, density of 2120 kg/m³, surface tension of 0.123 J/m²^[5], $K_{a,\text{sp}} =$

$2.24 \times 10^{-9} \text{ mol}^2 \text{ L}^{-2}$ at 37°C ^[6], molecular volume of $1.14 \times 10^{-28} \text{ m}^3$, molecular diameter of $4.85 \times 10^{-10} \text{ m}$. BRU has a molecular weight of 0.1721 kg/mol , density of 2310 kg/m^3 , surface tension of $0.068 \text{ J/m}^{2[7]}$, $K_{a,sp} = 2.74 \times 10^{-7} \text{ mol}^2 \text{ L}^{-2}$ at 37.5°C ^[8], molecular volume of $1.24 \times 10^{-28} \text{ m}^3$ and molecular diameter of $5.0 \times 10^{-10} \text{ m}$.

The rate of homogeneous nucleation of COM for $S = \sqrt{12} = 3.5$ (maximum S reported in^[2]) at 37°C according to eq. (6) is: $J_{\text{hom}} = 3.7 \times 10^{37} \exp(-4722) \sim 0$.

The rate of homogeneous nucleation of BRU for $S = \sqrt{2.5} = 1.6$ (maximum S reported in^[2]) at 37°C is: $J_{\text{hom}} = 3.2 \times 10^{37} \exp(-2178) \sim 0$.

A nucleation rate of 1 nucleus in 1 cm^3 per second, i.e., $J = 10^6 \text{ m}^{-3} \text{ s}^{-1}$, can be considered as the threshold for the onset of homogeneous nucleation. This rate is achieved when the supersaturation S with respect to COM and BRU is 35.9 and 13.6, respectively.

The critical nucleus of COM at $S = 3.5$ according to eq. (9) consists of 1257 "molecules" (ion pairs) and has a diameter of $6 \times 10^{-9} \text{ m}$. The critical nucleus of BRU at $S = 1.6$ consists of 4757 "molecules" (ion pairs) and has a diameter of $11 \times 10^{-9} \text{ m}$.

DISCUSSION

The urine of most people is supersaturated with respect to COM and BRU, the predominant constituents of kidney stones. However, only small fraction of people suffer from urolithiasis.

The first step in stone formation is the establishment of a tiny stable nucleus of a solid compound either in the liquid volume inside the kidney or on an inner wall of the kidney. A nucleus formed in the liquid volume must be retained within the kidney and grow to a macroscopic size.

Spontaneous unaided formation of a stable nucleus of COM or BRU in a liquid volume, this is by the mechanism of the homogeneous nucleation, only occurs at urinary supersaturations much higher than conceivable in any individual. Therefore the present analysis based on the theory of precipitation indicates that kidney stones cannot originate by homogeneous nucleation.

A necessary condition for the formation of solid phase nuclei in bulk urine is the presence of efficient substrates for nucleation. Spontaneous formation of crystals in urine can occur when value of the factor $f(\Theta)$ in eq. (7) is equal or lower than 0.015 for COM and 0.033 for BRU. Such low values of the factor $f(\Theta)$ indicate that substrates which are highly efficient in promoting nucleation must be present for the solid crystalline phase to appear. The phenomenon of crystalluria demonstrates that under special conditions macroscopic crystals with size up to $35 \times 10^{-8} \text{ m}$ and concentration of about $2 \times 10^5 \text{ m}^{-3}$ can originate in bulk urine^[9]. This concentration of crystals is typical for heterogeneous nucleation.

The critical nucleus is very small and can be retained

in the kidney after formation directly on the kidney wall or after attachment to the wall following formation in the liquid phase. However, some renal stones do not attach to the kidney wall. The nuclei of these stones must have originated in a cavity with poor urodynamics, and as they grew they formed an agglomerate that was large enough not to be washed from the kidney.

Nuclei formed in urine and retained in the kidney reach a macroscopic size by the accretion of additional building units (ions or ion pairs) and by subsequent agglomeration. The development of nuclei is strongly influenced by crystal growth modifiers naturally present in the urine that impede or completely stop solute attachment to the nucleus. Inhibitors, such as citrate, chondroitin sulphate, serum albumin, transferrin, osteopontin and Tamm-Horsfall protein^[10,11], interact with COM crystal surfaces and impede growth. Protein lysozyme and lactoferrin, which occur in the organic matrix of renal stones, promote the growth of COM crystals^[12]. Citrate, phytate, pyrophosphate and polyphosphates are effective inhibitors of BRU crystallization^[13,14].

Nuclei that are formed and retained in the kidney can reach macroscopic size only in the absence of growth inhibitors and/or the presence of growth promoters.

Renal stones composed of COM and/or BRU are formed only in the case that: (1) urine is supersaturated with respect to these compounds; (2) efficient substrates for solid phase nucleation (heteronuclei) are present; and (3) inhibitors of crystallization are absent and/or promoters of crystallization are present. In the presence of suitable nucleation substrates and a deficiency of inhibitors, higher urinary supersaturation enhances formation and the development of stones. Urinary supersaturation *per se* is a necessary but not a sufficient condition for urolithiasis and is therefore not a reliable diagnostic measure of the risk of stone formation. If conditions of stone formation (2) and (3) are fulfilled the magnitude of supersaturation indicates the probability of nephrolithiasis.

COMMENTS

Background

The supersaturation of urinary compounds has been considered during long time as a key risk factor for renal lithiasis. Recently it has been demonstrated that urinary supersaturation of calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate varied widely among healthy individuals and stone formers.

Research frontiers

The previously presented studies have been developed exclusively using information related to urinary biochemical parameters of patients and healthy individuals and checking that the values of supersaturation do not allow a good discrimination between both groups.

Innovations and breakthroughs

This study analyzes, using the classical theory of crystalline nucleation, the possibility of formation of crystals of COM or brushite (BRU) in human urine, as

a function of supersaturation.

Applications

This study demonstrates that the formation of COM and/or BRU renal calculi in urine supersaturated with these substances can only take place in the presence of efficient substrates for the nucleation of the corresponding solid phases (heteronuclei) and in the absence or deficit of crystallization inhibitors. Therefore, supersaturation is a necessary but not sufficient condition for the development of these stones. Supersaturation is therefore not a reliable diagnostic measure of the risk of stone formation. Nevertheless, in the presence of heteronuclei and crystallization inhibitory deficit, the magnitude of supersaturation may indicate the probability of nephrolithiasis. Identification of nucleation promoters and deficit of crystallization inhibitors is therefore very important as a diagnostic aspect to avoid urolithiasis.

Peer-review

The paper deals with theory of renal stones development; the paper is well written, clear and concise.

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Randomized Clinical Trial

Combined urethral and suprapubic catheter drainage improves post operative management after open simple prostatectomy without bladder irrigation

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Informed consent statement: All participants gave their written informed consent before inclusion in the study.

Conflict-of-interest statement: I have no conflicts of interest to declare.

Data sharing statement: The author on request will provide the raw data on which the study results were derived.

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Abstract

AIM

To compare outcomes after open simple prostatectomy without bladder irrigation, in subjects drained by combined 2-way urethral catheter and suprapubic catheter (SPC) *vs* those drained by 2-way urethral catheter only.

METHODS

A total of 84 participants undergoing Freyer's simple prostatectomy over an 18-mo period were randomized into 2 groups ($n = 42$). Subjects in group 1 were managed with 2-way urethral catheter and *in situ* 2-way SPC while subjects in group 2 had a 2-way urethral catheter drainage only. In group 1 subjects, the SPC was spigotted and only used for drainage if there was clot retention. The primary outcomes were number of clot retention episodes, and number of clot retention episodes requiring bladder syringe evacuation. Other secondary outcomes evaluated were blood loss, requirement of extra analgesics, duration of surgery, hospital stay and presence or absence of post-op complications.

RESULTS

The mean age in the groups was $65.7 (\pm 7.6)$ in group 1 *vs* $64.8 (\pm 6.8)$ in group 2. The groups were similar with respect to age, prostate specific antigen, prostate volume, blood loss, duration of surgery, blood transfusion and overall complication rate. However statistically significant differences were observed in clot retention episodes between group 1 and 2: $0.8 (\pm 1.5)$ *vs* $3.5 (\pm 4.4)$, $P < 0.000$, clot retention episodes requiring evacuation with bladder syringe $0.4 (\pm 0.9)$ *vs* $2.6 (\pm 3.8)$, $P = 0.001$, requirement of extra analgesics $0.4 (\pm 0.5)$ *vs* $4.0 (\pm 1.5)$, $P < 0.000$ and duration of admission $8.6 \text{ d } (\pm 1.2)$ *vs* 7.3

d (± 0.6), $P < 0.000$.

CONCLUSION

Subjects drained with a combination of urethral and SPCs have fewer clot retention episodes and reduced requirement of extra analgesics but slightly longer hospital stay.

Key words: Open suprapubic prostatectomy; Catheter drainage; Clot retention; Post operative outcome; Benign prostatic hyperplasia

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Core tip: Most urologists will agree that the most worrisome post operative challenge after open suprapubic prostatectomy (OSP) is post operative haemorrhage and the attendant clot retention. This paper seeks to show that the use of a combination of suprapubic and urethral catheters as opposed to using only a urethral catheter to drain the bladder after OSP is associated with reduced clot retention episodes, reduced clot retention episodes requiring bladder syringe evacuation and therefore less post operative morbidity.

Obi AO. Combined urethral and suprapubic catheter drainage improves post operative management after open simple prostatectomy without bladder irrigation. *World J Clin Urol* 2017; 6(2): 44-50 Available from: URL: <http://www.wjgnet.com/2219-2816/full/6/i2/44.htm> DOI: <http://dx.doi.org/10.5410/wjcu.v6.i2.44>

INTRODUCTION

Despite the advent of transurethral resection of the prostate (TURP)^[1], holmium laser enucleation of the prostate (HoLEP)^[2] and other minimally invasive procedures, open simple prostatectomy (OSP) still remains a common treatment option for bladder outlet obstruction due to benign prostatic hypertrophy (BPH)^[3-5], especially in the developing world. OSP is usually indicated in patients with large prostates above 80-100 g, patients with diverticular, large cystoliths, where the facilities and skills for less invasive procedures are not available or due to patient preference^[3,4,6]. In developed countries TURP and Laser prostatectomy account for most procedures^[3,4,6] but in the developing world OSP either in the form of Freyer's transvesical or Millin's retropubic prostatectomy is the commonest treatment modality^[3-5,7].

The most worrisome post operative challenge after OSP is post operative haemorrhage and the attendant clot retention. Tinckler^[8] has pointed out that, apart from general patient management, patient care following OSP is mainly concerned with ensuring uninterrupted drainage of urine and blood from the lower urinary

tract until normal haemostasis is attained, avoiding accumulation of blood and clot retention. The urethral drainage catheter is frequently blocked by blood clots in the immediate post operative period leading to painful clot retention episodes requiring repeated clot evacuation and occasionally a return to the operating room for either cystoscopic evacuation or re-exploration with its attendant risks. Clot retention rates as low as 4.3%-8%^[4,9,10] and as high as 47%^[5] have been documented. Also re exploration rates as high as 4.3%^[4] have been reported for recalcitrant clot-retention in patients undergoing OSP. Byrne^[11] observed that a significant percentage of deaths that occur secondary to haemorrhage after OSP can be attributed to inadequate catheter drainage of the bladder.

Therefore effective drainage of the bladder after OSP is key to a smooth post operative course and successful outcome. Measures to drain the bladder and deal with the problem of clot retention in the post operative period after OSP have included such things as the suprapubic double glass tube of Cabot^[12], the use of various types of wide bore catheters such as the perineal tube of Fuller^[13], the rusch red rubber rectal catheter used by Plawker *et al*^[14], and special suction devices^[15]. In contemporary practice however most urologists use continuous bladder irrigation (CBI) through a 3 way catheter^[16-18] or *via* a combination of 2 way urethral catheter and a suprapubic catheter (SPC)^[4,6,19]. Some however practice non irrigation and use only a 2 way urethral catheter to drain the bladder^[10,20,21]. Open simple prostatectomy without continuous bladder irrigation has been shown to be safe^[7,10,20,21] and is our current practice. Manual evacuation of clots with the 60cc catheter tip syringe (bladder syringe) may be an adjunct to any of the above measures. In difficult cases there might be need to return to the theatre for cystoscopic evacuation or outright re exploration.

We hypothesized that on a policy of non irrigation, the addition of an *in situ* SPC acting as a safety valve against clot retention will greatly simplify post operative management after OSP and that the outcome will be better than using only a 2-way urethral catheter. We therefore conducted a prospective 2-arm open label randomized trial comparing patients managed post operatively on combined urethral and *in situ* SPC vs patients managed on 2 way urethral catheter drainage only. To the best of our knowledge there is no randomized study comparing these two modalities in patients managed without bladder irrigation.

MATERIALS AND METHODS

Following institutional research ethical board review and approval, 84 participants undergoing Freyer's simple prostatectomy at Federal Teaching Hospital Abakaliki, Ebonyi State, Nigeria and Alpha Specialist Hospital (Urology Centre), Enugu Nigeria over an 18 mo period, January 2014 to June 2015 were randomized using

prelabelled sealed envelopes into 2 groups. This was a prospective 2-arm parallel, open-label randomized trial conducted in compliance with the principles enunciated in the Helsinki declaration. The statistical review of the study was done by a biomedical statistician.

The study power was set at 95%, *i.e.*, $(1 - \beta) = 0.95$ and at a level of significance, α , of 0.01% to sufficiently detect a difference of 8%^[4,9,10] vs 47%^[5] in the proportion of those developing clot retention after open simple prostatectomy without bladder irrigation, in subjects drained by combined 2-way urethral catheter and SPC vs those drained by 2-way urethral catheter only.

The sample size required to detect the above effect size was determined using the following formula^[22]; $n = \{f(\alpha, \beta) [P_0(100 - P_0) + P_1(100 - P_1)]\} / (P_0 - P_1)^2$.

Where P_0 = proportion of participants in Group 2 expected to develop clot retention = 47%; P_1 = proportion of participants in Group 1 expected to develop clot retention = 8%. $f(\alpha, \beta) = 17.8$.

This returned a sample size of approximately 40 participants per arm of the study and 80 participants in both arms.

Group 1 patients were managed post operatively with combined 2 way urethral catheter drainage and *in situ* 2 way SPC while group 2 patients were managed post operatively with only 2 way urethral catheter drainage. Informed consent was obtained from all patients before surgery. Prior to surgery detailed clinical history of all patients was documented. Indications for surgery were severe lower urinary tract symptoms; IPSS (International Prostate Symptom Score > 19) and acute urinary retention necessitating urethral catheterization. Preoperative laboratory work up included urinalysis, urine microscopy culture and sensitivity, complete blood count, platelet count, prostate specific antigen (PSA), serum electrolyte urea and creatinine (S/E/U/Cr) estimation, abdominopelvic ultrasound scan, chest X-ray and electrocardiogram. Patients with PSA above 4 ng/mL were subjected to transrectal prostate biopsy and operated on only, if the result showed BPH. Sterile urine was ensured as well as normal platelet count and S/E/U/Cr. Pre-operative hemoglobin levels were optimized to at least 11.5 g/dL.

Operative technique

All patients had Freyer's transvesical prostatectomy done in standard fashion. All the surgeries were done by the author who had 12 years post fellowship experience at the commencement of the study. Patients were administered *I.V.* ceftriaxone 1 g and *I.V.* metronidazole 500 mg 15 min prior to surgery. These antibiotics were continued till the 4th post operative day following which, patients were converted to oral ciprofloxacin 500 mg bid till post operative day 10.

All surgeries were done under regional anesthesia (spinal or epidural). The bladder was assessed *via* a pfannenstiel incision and opened transversely in its lower half between two stay sutures. After finger

enucleation of the prostatic adenoma haemostasis was secured by running 2/0 polyglactin suture of the bladder neck between the 5 and 7 o'clock positions. Additional bleeding points were either electro fulgurated or suture ligated. The prostatic fossa was not packed. A size 22F, 2 way silicone Foley urethral catheter was introduced into the bladder. Its balloon was inflated to 40 mL within the bladder and used to apply traction against the bladder neck by means of gauze bandage tied to the catheter and pushed snugly against the penile tip. This traction was maintained at the end of surgery by strapping the catheter to the patients thigh with plaster. The decision on whether or not to add a SPC was taken at the point of closing the bladder by an independent investigator, using prelabelled sealed envelopes. The SPC (size 22F) was sited at the dome of the bladder in group 1 patients and brought out through a separate stab incision of the skin in the midline about two finger breaths above the pfannenstiel incision. The SPC was retained with 15 mL sterile water for injection and spigotted. The bladder was closed in 3 layers and the wound washed with normal saline. A perivesical wound drain of size 22F Foley catheter was placed in the perivesical space and the abdominal wound was closed in layers. The skin was closed with subcuticular 2/0 polyglactin suture. Traction on the bladder neck was released fully by 24 to 36 h. None of the patients had continuous bladder irrigation. Post operatively patients received, alternately 8 hourly intramuscular tramadol and pentazocine for analgesia.

Data collected and analyzed include demographic and clinical data such as age, prostate volume, PSA, pre and post operative hemoglobin, duration of surgery, clot retention episodes, clot retention episodes requiring evacuation with the 60 cc bladder syringe, requirement for extra analgesics, blood transfusion, hospital stay and complications. The primary outcomes were number of participants with clot retention episodes, and number of clot retention episodes requiring bladder syringe evacuation. Secondary outcomes evaluated were blood loss, requirement of extra analgesics, duration of surgery, hospital stay and presence or absence of post-op complications. Post operative hemoglobin was estimated on post operative day 2. Hospital stay was calculated from the day of operation to the day of discharge. For group 1 patients the SPC was left *in situ* as a safety valve. It was deployed for drainage of the bladder only when the urethral catheter was blocked by clots. The SPC was removed when the urine became consistently clear, usually by post operative day 2 or 3. The suprapubic cystostomy site was dressed and allowed to close naturally. The urethral catheters were spigotted by post operative day 5 or 6 and removed 24 h later. Patients in group 1 required an additional day or two to ensure closure of the SPC site. All enucleated prostates were sent for histology.

Statistical analysis

Data were analyzed using SPSS Version 16, Chicago IL,

Table 1 Demographic and clinic characteristics of groups 1 and 2 patients

Reps	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)	P value
Patients (n)	42	42	
Age (yr)	65.7 (\pm 7.6)	64.8 (\pm 6.8)	0.598
Prostate volume (mL)	85.6 (\pm 49.1)	89.3 (\pm 42.1)	0.715
PSA (ng/mL)	15.3 (\pm 15.0)	12.6 (\pm 15.3)	0.417
Duration of surgery (min)	102.9 (\pm 18.8)	100.7 (\pm 14.9)	0.555
Blood transfusion (pints)	0.4 (\pm 0.6)	0.6 (\pm 0.9)	0.277
Clot retention episodes	0.8 (\pm 1.5)	3.5 (\pm 4.4)	0
Clot retention episodes requiring bladder syringing	0.4 (\pm 0.9)	2.6 (\pm 3.8)	0.001
Requirement for extra analgaesic	0.4 (\pm 0.5)	4.0 (\pm 1.5)	0
Change in haemoglobin (g/dL)	1.9 (\pm 1.2)	2.1 (\pm 1.1)	0.408
Duration of admission (d)	8.6 (\pm 1.2)	7.3 (\pm 0.6)	0

PSA: Prostate specific antigen.

United States. Student's *t* test was used to determine whether the observed differences in means was significant. Categorical variables were analyzed with the χ^2 test. *P* < 0.01 was taken as significant.

RESULTS

There were 42 patients in each group. The mean age of the groups was 65.7 (\pm 7.6) in group 1 vs 64.8 (\pm 6.8) in group 2. The groups were similar with respect to age, PSA, prostate volume, change in hemoglobin level, duration of surgery, blood transfusion and overall complication rate. However statistically significant differences were observed in clot retention episodes, clot retention episodes requiring evacuation with the 60 mL bladder syringe, requirement of extra analgesics and duration of admission (Table 1). Abnormally high PSA values were observed in some patients. However these patients had negative prostate biopsies prior to surgery and the resected specimens also had negative histology.

Overall complication rate showed that 33.3% of patients in group 1 and 35.7% of patients in group 2 had complications. The difference was not statistically significant. Detailed evaluation of complications showed a total of 39 complications; 24 (61.5%) in group 1 and 15 (38.5%) in group 2 (Table 2). Many patients in group 1 had more than one complication thus explaining the disparity in overall and actual complication rates. Post prostatectomy lower urinary tract symptoms (frequency, urgency, urge incontinence and dribbling) was the commonest complication accounting for 12 (30.8%), followed by urinary tract infection 10 (25.6%) and secondary haemorrhage 5 (5.1%). Details of complications are shown in Table 2. Persistent suprapubic urinary fistula was observed in 3 patients (8.1%) in group 1. No patient in group 2 had a urinary fistula. Urinary fistulas were managed by continuous

bladder drainage and treatment of urinary tract infection (UTI). Additional measure was to close the fistula with 2/0 nylon suture after freshening the edges. These 3 patients were discharged home on catheter. There was no mortality. There were no incidental prostate carcinomas. Follow up period is currently 7.13 (\pm 1.91) mo.

DISCUSSION

There has been a paradigm shift in the management of BPH in the last four decades towards less invasive procedures such as TURP^[1] and Laser prostatectomy^[2], especially for prostates less than 80-100 g. In the developed world these minimally invasive transurethral procedures account for most of the procedures, while open suprapubic prostatectomy (OSP) accounts for only 3%-40% of procedures^[3,23]. The reverse is the case in the developing world largely because of absence of skilled manpower and technology for minimally invasive transurethral procedures^[7]. It has also been noted that more and more patients are presenting these days with prostates in the 80 to 100 g range because of the increasing use of medical treatment or watchful waiting^[2,23]. Thus there will always be a place for OSP whether in the developed or developing world. While OSP is more invasive and requires an abdominal incision with subsequently longer hospitalization and convalescence than transurethral techniques, it results in an excellent functional outcome and low reoperation rates^[3,18,24].

Morbidity and mortality after OSP is closely tied to the problem of clot retention and adequacy of bladder drainage^[8,11]. Clot retention if left untreated, can lead to severe pain, tachycardia, azotemia, hypertension and bladder rupture^[14,25].

Traditionally effective drainage of the bladder and prevention of clot retention after OSP has been by means of continuous bladder irrigation (CBI) with normal saline through a 3 way urethral catheter^[16-18] or via a combination of 2 way urethral catheter and a SPC^[4,19] with or without manual evacuation of clots with the 60 cc catheter tip syringe. There might be a resort to cystoscopic evacuation or outright re-exploration if the latter fails. Some studies^[20,21] have queried the need for CBI pointing out, that clot retention still frequently occurs even under CBI and that there is a risk of bladder rupture with unregulated inflow of irrigant. CBI is also associated with increased workload on the staff and increased financial burden to the patient. OSP without CBI has been shown to be safe^[7,10,20,21] and is our current practice. Under this non irrigation protocol two options exist for draining the bladder; One is the use of a 2 way urethral catheter alone and the other is the use of a combination of 2 way urethral catheter with addition of a SPC as a safety valve against clot retention. This study compares post operative outcomes in patients managed with combined SPC and 2 way urethral catheter and those drained by 2 way urethral catheter only. All patients were managed without CBI.

Table 2 Overall complication rate and details of complications by Clavien Dindo grade observed in both groups *n* (%)

Complications	Clavien Dindo grade	Group 1	Group 2	Total	<i>P</i> value
Overall complications		14 (33.3)	15 (35.7)	29 (34.5)	0.5
Post prostatectomy (LUTS)	II	5 (12.8)	7 (17.9)	12 (30.8)	0.378
Post prostatectomy UTI	II	8 (20.5)	2 (5.1)	10 (25.6)	0.044
Secondary hemorrhage	II	4 (10.3)	1 (2.6)	5 (12.8)	0.18
Surgical site infection	IIIa	3 (7.7)	1 (2.6)	4 (10.3)	0.308
Persistent suprapubic fistula	IIIa	3 (7.7)	-	3 (7.7)	0.12
Delirium	II	-	2 (5.1)	2 (5.1)	0.247
Left ventricular failure	IVa	-	1 (2.6)	1 (2.6)	0.5
Cardiac arrhythmia	IVa	-	1 (2.6)	1 (2.6)	0.5
Septicemia	II	1 (2.6)	-	1 (2.6)	0.5
Total		24 (61.5)	15 (38.5)	39 (100)	

LUTS: Lower urinary tract symptoms; UTI: Urinary tract infection.

The mean age of the groups was respectively, 65.7 (\pm 7.6) in group 1 vs 64.8 (\pm 6.8) in group 2. These means are similar to the mean age of patients undergoing OSP^[4,20]. The age difference between the two groups was not statistically significant, $P = 0.598$. The difference between the two groups with respect to prostate volume, PSA and duration of surgery was also not statistically significant (Table 1). However statistically significant differences were observed in the mean clot retention episodes (CREs), clot retention episodes requiring evacuation with the 60 mL bladder syringe, requirement of extra analgesics and duration of admission.

The mean CREs in group 1 was much lower than that of group 2; 0.8 (\pm 1.5) (range 0-6) vs 3.5 (\pm 4.4) (range 0-16), $P = 0.000$. CREs of between 0.9% to 47% have been reported by various authors^[1,5,9,10]. The difference in CREs between the groups is not surprising because group 1 patients had an alternative route for bladder drainage in the event of clot retention. In this group the spigotted SPC was opened and connected to a urine bag once the first clot retention episode occurred. The SPC was then left open to drain the bladder alongside the 2 way urethral catheter until the urine became clear enough for the SPC to be removed. Formed clots naturally gravitate to a dependent position in the bladder and block the urethral draining catheter leaving the SPC which is sited at the dome of the bladder free to drain the bladder, while clot lysis is ongoing.

In the presence of clot retention, some clots may pass spontaneously or pass following milking of the urethral catheter. When these fail the next option is to evacuate the clots using the 60 cc bladder syringe. Evaluation of CREs requiring evacuation with the bladder syringe between the two groups showed that mean CREs requiring bladder syringe evacuation was 0.4 (\pm 0.9) (range 0-4) in group 1 compared to a mean of 2.6 (\pm 3.8) (range 0-14) in group 2. This difference was statistically significant, $P = 0.001$. Patients are better off with fewer CREs requiring evacuation with the bladder syringe. For one, clot evacuation can be tasking, time

consuming and sometimes inefficient, because the catheter walls tend to collapse under the negative pressure of the bladder syringe^[14]. There is also the risk of introducing infection into the bladder by too frequent flushing out of clots. None of the groups required reoperation for clot retention or cystoscopic evacuation and there was no mortality.

Clot retention is not just associated with increased demand on the time and resources of the staff but is also associated with increased patient discomfort, post operative pain and requirement of extra analgesic. The mean demand for extra analgesic between the two groups varied considerably. While it was 0.4 (\pm 0.5) (range 0-2) for group 1, it was 4.0 (\pm 1.5) (range 0-7) for group 2. This difference was statistically significant, $P = 0.000$. The reduced demand for extra analgesic in group 1 is in keeping with the fewer CREs and CREs requiring evacuation with the bladder syringe in this group. A cost analysis reveals an extra cost of approximately 42USD per patient for dealing with the burden of extra clot retention episodes and clot retention episodes requiring evacuation with the 60 cc bladder syringe observed in group 2. This is broken down into; cost of SPC-1.2USD, urine bag-0.5USD, 60 cc bladder syringe(average of 3/patient)-4.5USD, Normal saline for flushing the catheters(average, 4L/patient)-3.6USD, extra analgesic (average 8 ampoules of tramadol/patient)-3.0USD, extra demand on nursing services-20USD, change of soiled beddings and dressings-9USD. In a resource poor environment this extra 42USD can be a significant economic burden to the patient.

Mean blood transfusion was lower in group 1 compared to group 2; 0.4 (\pm 0.6) vs 0.6 (\pm 0.9) respectively. Also the mean change in hemoglobin was lower in group 1 compared to group 2; 1.9 (\pm 1.2) g/dL vs 2.1 (\pm 1.1) g/dL. These differences approached but did not reach statistical significance. P values, 0.277 and 0.408 respectively. Blood transfusion rates after OSP can vary greatly. While some authors claim zero transfusion^[10,21]. Most large series report blood transfusion in the range of 1% to 57.1%^[3,6,7]. Bleeding

after OSP occurs not just because of inadequate haemostasis but also because clots and clot retention cause over distension of the bladder. Over distention provokes further bleeding because the bladder and prostatic fossa are prevented from contracting down on the bleeding points. Therefore any measure that can reduce clot retention will reduce post operative bleeding. In this study the mean blood transfusion and change in hemoglobin concentration was lower in group 1 in keeping with the reduced CREs and CREs requiring evacuation observed in this group.

Overall complication rate in this study was 34.5%. This is similar to the 30% and 31.3% rates reported in some other series^[18,24]. Both groups were similar in terms of overall complication rate with 33.3% of patients in group 1 and 35.7% of patients in group 2 having complications $P = 0.500$ (Table 2). However detailed analysis of actual complications showed that there were more complications in group 1 than group 2 because some patients in this group had more than one complication (Table 2). Post prostatectomy lower urinary tract symptoms (LUTS) namely frequency, urgency, urge incontinence and dribbling was the commonest complication in both groups accounting for 30.8% of the overall complications. It was slighter commoner in group 2 than group 1; 7 (17.9%) vs 5 (12.8%). Others have also observed worrisome post prostatectomy LUTS to be a common complication after OSP^[1,9]. A range of 6.7% to 11.1% has been reported^[1,9] which is slightly lower than observed in this study. The condition usually resolves with keggel exercises over a short period of time with or without antimuscarinics. UTI has to be ruled out as a cause and treated. In this series all cases resolved within one month after discharge. The next most common complication was post prostatectomy urinary tract infection which accounted for 25.6% of complications. This is lower than the 40% figure reported by Bapat *et al*^[9] after Freyer's prostatectomy. It was seen more in group 1 than group 2; 8 (20.5%) vs 2 (5.1%). Post prostatectomy haematuria (secondary hemorrhage) was also commoner in group 1 than group 2; 4 (10.3%) vs 1 (2.6%). Haematuria may be a complication of UTI. The higher incidence of these two complications in group 1 may be related to the presence of the SPC. The suprapubic ostium may have been a source of bacterial entry into the urinary tract. Persistent suprapubic urinary fistula was observed in 3 patients (7.7%) in group 1. No patient in group 2 had a suprapubic urinary fistula. The urinary fistulas were managed by continuous bladder drainage and treatment of UTI if present. These three patients had UTI. In these three patients the suprapubic ostium was sutured and the patients discharged home on catheter. Mean duration of admission was 8.6 d (± 1.2) in group 1 and 7.3 d (± 0.6) in group 2, $P = 0.000$. This statistically significant difference in duration of admission between the two groups can be attributed to the extra time it took for the suprapubic fistulae to close in group 1 patients. There was no mortality in this series.

Draining the bladder with a combination of urethral and SPC is associated with a smoother post operative course because of fewer clot retention episodes and clot retention episodes requiring bladder syringe evacuation. It is also associated with reduced requirement of extra analgesic. These advantages have to be weighed against the disadvantage of an occasional persistent suprapubic fistula resulting in slightly longer hospital stay.

COMMENTS

Background

Despite the advent of newer technologies for treating benign prostatic hypertrophy (BPH), open simple prostatectomy (OSP) still remains a common treatment option for bladder outlet obstruction due to BPH. Currently some urologists advocate non bladder irrigation after OSP and they site several disadvantages of bladder irrigation such as cost, increased staff workload, patient discomfort, risk of bladder rupture, prolonged immobilization, and perhaps more importantly that it does not prevent clot retention. Two options exist for draining the bladder after non irrigated OSP; one is the use of a urethral catheter only and the other is to use a combination of urethral and suprapubic catheters (SPCs) so that the SPC acts as a safety valve should there be recalcitrant clot retention. It is expected that this latter method will guarantee uninterrupted drainage of urine and blood from the lower urinary tract until normal haemostasis is attained, avoiding accumulation of blood and clot retention.

Research frontiers

This study is important because it helps to support the advocacy for OSP without bladder irrigation. The disadvantages of bladder irrigation after OSP have already been clearly spelt out.

Innovations and breakthroughs

To the best of the knowledge this is the only study evaluating in a randomized fashion, bladder drainage after OSP.

Applications

The practical applications of using a combination of urethral and SPCs to drain the bladder after OSP is that because it is associated with fewer clot retention episodes, it requires less monitoring. It is therefore useful in settings where there is less manpower such as private hospitals and in developing countries. It is also cheaper because it is associated with less requirement of extra analgesic, need to evacuate clots and blood transfusion.

Peer-review

The subject of the study is original and the manuscript is well written.

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